CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201292Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 201292 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: GILOTRIF Established/Proper Name: Afatinib Dosage Form: Tablet		Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Deanne Varney		Division: DOP2

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is July 15, 2013 • Action Taken July 12, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO Burst

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval – 7/12/2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	7/11/2013
• Original applicant-proposed labeling	11/14/2012
• Example of class labeling, if applicable	Tarceva, 5/14/13

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	7/11/2013 – Patient Information Sheet attached to PI
• Original applicant-proposed labeling	11/14/2012 – Patient Information Sheet attached to PI
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	4/26/2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	Proprietary Name Conditionally Acceptable – 4/19/2013 Proprietary Name Review – 4/19/2013
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 12/27/2012 ☒ DMEPA 4/9/2013 ☒ DMPP/PLT 4/29/2013 ☒ ODPD (DDMAC) 4/29/2013 ☐ SEALD ☐ CSS ☒ Other reviews QT-IRT: 3/27/2013 Maternal Health: 5/14/2013
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	RPM Filing Review: 12/20/12 ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC If PeRC review not necessary, explain: This product has orphan designation for the requested indication. • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	7/11/2013 (DARRTS 7/12/2013) 7/10/2013 7/8/2013 7/3/2013 7/2/2013 (2) 6/28/2013 (2) 6/6/2013 6/5/2013 (2) 6/4/2013 6/3/2013 (DARRTS 6/4/2013) 5/29/2013 5/28/2013 5/16/2013 (2) 5/3/2013 (DARRTS 5/6/2013) 5/2/2013 (DARRTS 5/3/2013) 4/30/2013 4/25/2013 4/24/2013 4/23/2013 4/19/2013 4/17/2013 (DARRTS 4/18/2013) 4/12/2013 4/8/2013 4/4/2013 4/3/2013 4/2/2013 4/1/2013 3/25/2013 3/21/2013 3/13/2013 3/11/2013 (2) 3/5/2013 2/27/2013 2/22/2013 2/20/2013 2/4/2013 1/28/2013 (DARRTS 1/30/13) 1/25/2013 1/24/2013 1/23/2013 1/18/2013 1/11/2013 1/8/2013 12/20/2012 12/13/2012 (2) 11/28/2012 11/20/2012 11/19/2012
Internal memoranda, telecons, etc.	7/3/2013 6/10/2013 6/7/2013 6/5/2013

	5/1/2013 4/25/2013 (DARRTS 4/26/2013) 4/25/2013 (DARRTS 4/26/2013) 4/24/2013 (DARRTS 4/25/2013) 4/19/2013 4/17/2013 (DARRTS 4/19/2013) 4/8/2013 2/7/2013 (DARRTS 2/8/13) 2/6/2013 1/4/13 12/13/2012 (DARRTS 12/20/12) 11/28/2012
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 10/10/2012 (DARRTS 10/16/12) 12/9/2011 (DARRTS 12/12/11) 12/15/2009 (DARRTS 2/2/10)
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 10/16/2008
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 7/12/2013
Division Director Summary Review *(indicate date for each review)*	☐ None 7/11/2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 6/20/2013
PMR/PMC Development Templates *(indicate total number)*	☐ None 2 (6/19/2013 and 7/3/2013)
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL review dated 6/20/2013
• Clinical review(s) *(indicate date for each review)*	4/22/2013 1/9/2013 (filing)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See clinical review page 15, dated 4/22/2013
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[6] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None Risk Management Review – 4/24/2013
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 6/28/2013 6/4/2013 5/13/2013 (2) 4/17/2013
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None 4/22/2013 (concurrence, see statistical review)
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None 4/22/2013 (concurrence, see statistical review)
Statistical Review(s) *(indicate date for each review)*	☐ None 4/22/2013 12/14/2012 (filing, with TL concurrence)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None 4/22/2013 (concurrence with clin pharm review)
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 4/22/2013 (concurrence with clin pharm review)
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 7/11/2013 4/22/2013 12/19/2012 (filing, with TL concurrence)
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 4/30/2013
• Supervisory Review(s) *(indicate date for each review)*	☐ None 4/29/2013
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 4/29/2013 12/17/2012 (filing, with TL concurrence)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 6/27/2013
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None 4/22/2013 (concurrence, see ONDQA review) 12/12/2012 (filing, with TL concurrence)
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 5/6/2013 (amendment) 4/22/2013 4/22/2013 (biopharm) 12/13/2012 (filing, with TL concurrence) (biopharm)
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See ONDQA review page 84, 4/22/2013
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 6/26/2013 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☒ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

EXCLUSIVITY SUMMARY

NDA # 201292 SUPPL # HFD #

Trade Name Gilotrif

Generic Name Afatinib

Applicant Name Boehringer Ingelheim Pharmaceuticals, Inc.

Approval Date, If Known PDUFA 7/15/13

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Deanne Varney
Title: Senior Regulatory Project Manager
Date: 7/10/2013

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEANNE R VARNEY
07/10/2013

PATRICIA KEEGAN
07/10/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 201292 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DOP2 PDUFA Goal Date: 7/15/13 Stamp Date: 11/15/2012

Proprietary Name: TBD

Established/Generic Name: Afatinib

Dosage Form: Tablet

Applicant/Sponsor: Boehringer Ingelheim

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

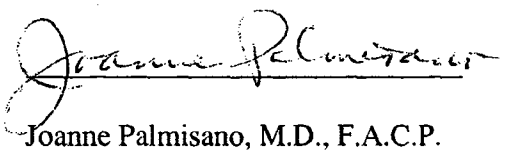
FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

DEBARTMENT CERTIFICATION

Certification Requirement Section 306(k)(1) of the Act 21 U.S.C. 355a(k)

Boehringer Ingelheim Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Signature: 

Name of Applicant: Joanne Palmisano, M.D., F.A.C.P.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: 24-Oct-2013

Mailing Address: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, July 11, 2013 12:08 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Gilotrif NDA 201292 - Labeling

Hi Ann,

Please find attached clean versions of the Gilotrif labeling. FDA has accepted all final edits proposed by BI.

Please submit the final draft labeling to your NDA by **COB today, July 11th,** with a courtesy copy to me via email. Please include clean and tracked versions.

Please confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

19 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) Immediately Following this Page

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/s/

DEANNE R VARNEY
07/12/2013

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, July 10, 2013 11:29 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: Gilotrif NDA 201292 - Labeling

Hi Ann,

Please find attached FDA's sixth round of proposed edits to the Gilotrif labeling.

Please review our proposed edits and comments to the Gilotrif labeling and determine if you are in agreement with the proposed edits. If so, please accept all edits and submit the final draft labeling to your NDA by **10AM on Thursday, July 11th,** with a courtesy copy to me via email.

If you have additional edits to propose, please accept the edits you agree with, make the requested changes plus any additional edits in track changes, and submit the counterproposal to your NDA by **10AM on Thursday, July 11th, 2013,** with a courtesy copy to me via email.

Please confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
07/10/2013

Varney, Deanne

From: Varney, Deanne
Sent: Monday, July 08, 2013 10:04 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Labeling

Hi Ann,

Please find attached FDA's fifth round of proposed edits to the afatinib PI and PPI. In addition to these edits, please update the Table of Contents and correct formatting as needed.

Please review our proposed edits and comments to the afatinib labeling and determine if you are in agreement with the proposed edits. Please accept all edits that you agree with, make any additional edits in track changes, and submit the updated labeling to your NDA by **3PM on Tuesday, July 9, 2013.**

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
07/08/2013

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, July 03, 2013 2:29 PM
To: 'ann.agnor@boehringer-ingelheim.com'
Subject: RE: Afatinib NDA 201292 - Proposed PMR

Hi Ann,

Thank you again for your quick turnaround time in responding to this PMR.

The clinical pharmacology team has reviewed your proposed timelines, and has a recommendation for an alternate timeline (please see below). However, we realize that you might feel these recommended timelines are not feasible. If that is the case and you would prefer to retain your originally proposed timeline, please provide justification for the milestone dates you provided.

Alternate Milestone Date Proposal:
Submit Draft Protocol (1 month before final protocol submission): November 2013
Final Protocol Submission: December 2013
Trial Completion: June 2015
Final Clinical Trial Report Submission: September 2015

Whichever route you choose (providing justification for your proposed dates or adopting those proposed by FDA), please submit this PMR and the proposed milestone dates (with justification if you retain yours) as a formal amendment to your NDA, along with the already agreed upon clinical PMC, by **COB on Friday, July 5th.**

Please confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Wednesday, July 03, 2013 12:03 PM
To: Varney, Deanne
Subject: RE: Afatinib NDA 201292 - Proposed PMR

Hi Deanne,

Attached is a courtesy copy of the NDA amendment submitted today (SEQ 0039) regarding PMR/PMC.

And *just in case* I don't hear from you later…Have a Happy 4th of July!

Kind regards,
Ann

From: Varney, Deanne [mailto:Deanne.Varney@fda.hhs.gov]
Sent: Tuesday, July 02, 2013 2:56 PM
To: Agnor,Ann (DRA) BIP-US-R
Subject: RE: Afatinib NDA 201292 - Proposed PMR

Hi Ann,

I realize I didn't give you a timeline to respond by. If it is at all possible to respond with proposed milestone dates by COB tomorrow (Wednesday the 3rd), that would be great. If not, please respond no later than 12PM on Friday the 5th.

And again, please call with any questions.

Thank you,
Deanne

From: Varney, Deanne
Sent: Tuesday, July 02, 2013 2:09 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Proposed PMR

Hello Ann,

Please find attached a proposed clinical pharmacology post-marketing requirement (PMR) that the FDA review team has determined is necessary.

The reasoning for this PMR is as follows:

In the registration trial it was observed that the median trough afatinib plasma concentrations in patients with mild and moderate renal impairment were 27% and 85% higher than those in patients with normal renal function, respectively. Patients with severe renal impairment may have even higher afatinib exposures, which could cause more toxicity.

Please review the attached PMR and propose dates for each of the four milestones that are outlined. Please note that missing goal dates will require you to provide justification for the delays, and such delays could result in enforcement actions. Therefore, you should provide some buffer time for unexpected difficulties in completing the scheduled milestones, and use due diligence in proposing the schedule taking into account time for recruitment of study institutions, IRB approvals, accrual rate, drop-out rate, etc.

Please submit this PMR and your proposed milestone dates as a formal amendment to your NDA, along with the already agreed upon clinical PMC. If you have any questions regarding this PMR, please let me know and I can arrange for a teleconference to discuss.

Please confirm receipt of this communication.

<< File: Afatinib NDA 201292_PMR.pdf >>

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
07/03/2013

TEAM MEETING MINUTES
July 3, 2013

New NDA 201292
Afatinib
Boehringer Ingelheim

Submission Date: November 14, 2012
Received Date: November 15, 2012
PDUFA Date: July 15, 2013

Proposed Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test

Current Review Team for NDA 201292:
Patricia Keegan, Director DOP2
Deanne Varney, Regulatory Health Project Manager
Karen Jones (CPMS)
Shakun Malik, Medical Officer
Anthony Murgo, Medical Officer (CDTL)
Jonathan Norton, Statistics
Kun He, Statistics (TL)
Runyan Jin, Clinical Pharmacology
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology (TL)
Dubravka Kufrin, Non-Clinical
Whitney Helms, Non-Clinical (TL)
Li Shan Hsieh, Quality
Liang Zhou, Quality (TL)
Ali Al Hakim, Quality (TL)
Jewell Martin, Quality (ONDQA RPM)
Angelica Dorantes, Biopharmaceutics TL
Elsbeth Chikhale, Biopharmaceutics Reviewer
Rosane Charlab Orbach, Genomics Reviewer

Consults for NDA 201292:
James Schlick, OSE Proprietary Name Reviewer and DMEPA Reviewer
Todd Bridges, DMEPA TL
Bob Pratt, DRISK
Cynthia Lacivita, DRISK TL
Kate Coyle, DPV
Corrinne Kulick, DPV TL

Quynh-Van Tran, OPDP Professional Reviewer
Shenee Toombs, OPDP, Consumer Reviewer
Lauren Iacono-Connors, OSI
Tammy Brent-Howard, Maternal Health
Carrie Ceresa, Maternal Health TL
Karen Dowdy, PLT
Barbera Fuller, PLT (TL)
Adel Abou-Ali, DEPI

CDRH Review Team for PMA:
Jennifer Shen

Review Status:

- Priority Review requested (PDUFA V --- 8 month review)
- Categorical Exclusion from environmental assessment requested
- Orphan designation granted; exempt from PREA
- Requested waiver of half-page Highlights
- The clinical development of afatinib has been conducted under INDs 67969 and 114002

Agenda Items:

1. Discuss Target Action Date and CDRH Review Status

Discussion: CDRH is still waiting on pending labeling from Qiagen, and thinks a target action date of July 12, 2013 will be feasible. The updated action date will be communicated to the necessary people.

2. Proposed Clinical Pharmacology PMR: Conduct a pharmacokinetic trial to determine the appropriate doses of afatinib in patients with moderate and severe renal impairment in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

Discussion: Currently with BI, requested proposed milestone dates by COB today (July 3, 2013). Clinical pharmacology will amend their review to include this PMR.

PMC: Submit the data from the final overall survival analysis from Study 1200.32 in order to better characterize the effects of afatinib treatment on overall survival.

PMC Milestone Date:
Final Submission of complete clinical trial report: 4/30/2014

Discussion: Already negotiated with BI

3. **Approval Letter**

Discussion: The approval letter has been cleared up through Dr. Pazdur, but will need to be re-cleared by SRT for the new PMR.

4. **Press Release and ASCO Burst:**

Discussion: On track.

5. **Labeling**

Discussion: BI's counterproposal was reviewed.

6. **Milestone Goals Remaining:**

Milestone	**8 month review July 15, 2013**
Acknowledgment Letter	November 29, 2012 ***Issued November 20, 2012***
Priority Review Determination/Filing Issues Identified Letter	January 14, 2013 ***Issued January 11, 2013***
Mid-Cycle Communication	February 28, 2013 ***Scheduled February 20, 2013***
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	April 19, 2013
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	April 26, 2013
Issue Discipline Review Letters	April 26, 2013
Late Cycle Meeting	May 7, 2013 *(Briefing package due 4/25/13)*
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 April 22, 2013 April 25, 2013 June 20, 2013 July 5, 2013 July 15, 2013
Compile and circulate Action Letter and Action Package	June 25, 2013
FINAL Action Letter Due	**July 15, 2013**

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/s/

DEANNE R VARNEY
07/03/2013

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, July 02, 2013 2:09 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Proposed PMR

Hello Ann,

Please find attached a proposed clinical pharmacology post-marketing requirement (PMR) that the FDA review team has determined is necessary.

The reasoning for this PMR is as follows:

In the registration trial it was observed that the median trough afatinib plasma concentrations in patients with mild and moderate renal impairment were 27% and 85% higher than those in patients with normal renal function, respectively. Patients with severe renal impairment may have even higher afatinib exposures, which could cause more toxicity.

Please review the attached PMR and propose dates for each of the four milestones that are outlined. Please note that missing goal dates will require you to provide justification for the delays, and such delays could result in enforcement actions. Therefore, you should provide some buffer time for unexpected difficulties in completing the scheduled milestones, and use due diligence in proposing the schedule taking into account time for recruitment of study institutions, IRB approvals, accrual rate, drop-out rate, etc.

Please submit this PMR and your proposed milestone dates as a formal amendment to your NDA, along with the already agreed upon clinical PMC. If you have any questions regarding this PMR, please let me know and I can arrange for a teleconference to discuss.

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

Afatinib NDA 201292 – Proposed PMR and PMC

Proposed Post-Marketing Requirement:

1. Conduct a pharmacokinetic trial to determine the appropriate doses of afatinib in patients with moderate and severe renal impairment in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*."

Proposed PMR Milestone Dates:
Submit Draft Protocol (3 months before final protocol submission): MM/YY
Final Protocol Submission: MM/YY
Trial Completion: MM/YY
Final Clinical Trial Report Submission: MM/YY

Agreed Post-Marketing Commitment:

2. Submit the data from the final overall survival analysis from Study 1200.32 in order to better characterize the effects of afatinib treatment on overall survival.

Agreed PMC Milestone Dates:
Final Clinical Trial Report Submission: April 2014

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/s/

DEANNE R VARNEY
07/02/2013

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, July 02, 2013 1:34 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Response to BI Information Request - Renal Impairment

Hi Ann,

In response to your request for information regarding how the numbers in the Renal Impairment section of 12.3 of the PI were derived, please see the below information from the clinical pharmacology team. Please let me know if you have any questions, and please confirm receipt.

We are providing the R code that was used to derive the renal impairment median values of trough concentration at steady state. Please note that the median values were updated to 27% and 85% instead of 14% and 37%. We only selected trough values obtained from the pivotal trial (1200.32) with a starting dose of 40 mg. The baseline creatinine clearance values were obtained from a population pk dataset (poppk-data1.xpt) located at "NDA201292/0000/m5/datasets/1200-28-32-33/analysis". The trough concentration data (poppkp.xpt) were obtained from the submission located at "NDA201292/0007/m5/datasets/1200-iss/analysis". Trough concentrations in this dataset are defined by the Sponsor as Day 15 trough concentration.

Below are R codes for calculating median values for renal impairment:

```
#population PK dataset: poppk-data1.xpt contains baseline CRCL values and patient's ID (PTNO)

library(foreign)

poppk1 <- read.xport("poppk-data1.xpt")

poppk1.1<-poppk1[!duplicated(poppk1$PTNO)=="TRUE",] # include first PTNO for baseline CRCL



## read data with trough conc on day15: poppkp.xpt contains trough concentration on Day15

poppkp<-read.xport("poppkp.xpt")



day15.all<-poppkp[,c("STUDY","PTNO","CPRESS","DOSEC","COMMENT")]

names(day15.all)[3] <- "CP_day15" # rename column

## merge popPK data and data with trough conc at day15

popall.day15<-merge(poppk1.1,day15.all,by=c("PTNO"), all=T)
```

```
## select starting dose with 40mg only

popday15.40mg<-subset(popall.day15, DOSEC==40)

##select Study 1200.32

popday15.40mg<-subset(popall.day15, STUDY=="1200_0032")

##############################################################################################
####################

#Note: popall.day15 contains all pk covariates including CRCL (renal function) and trough day 15 conc

##############################################################################################
#################

popall.day15.2<-popday15.40mg[!is.na(popday15.40mg$CRCL),]

## define cut-offs for renal function categories

popall.day15.2$CRCLC <- ifelse(popall.day15.2$CRCL >=90, "1", # "Healthy"

ifelse(popall.day15.2$CRCL >= 60, "2", # "Mild"

ifelse(popall.day15.2$CRCL >= 30, "3", #"Moderate"

"4" #"Severe"

      )

   )

  )

table(popall.day15.2$CRCLC)

# 1 2 3

# 79 130 20

## Median values of CRCL based on different renal function

tapply(X=popall.day15.2$CP_day15, INDEX=popall.day15.2[,c("CRCLC")], FUN=median)

# healthy (n=79) Mild (n=130) Moderate (n=20)

# median Trough Conc 23.80 30.15 44.10
```

Thank you,

Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
07/02/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 28, 2013

From: Deanne Varney, RPM, DOP2/OHOP/CDER/FDA

Subject: NDA 201292

TELECONFERNCE

Sponsor Attendees:

Dennis O'Brien, MD	Team Member, Drug Safety
James Segretario, PhD	Director, CMC Regulatory Affairs
Peter Stei, Dr. med. vet.,	Nonclinical Drug Safety
James Love, M. Stat.	Project Statistician
Ann Agnor, MS	Regulatory Affairs US
Pamela Strode	Executive Director, Regulatory Affairs

FDA Attendees:

Deanne Varney
Shakun Malik
Patricia Keegan
Gideon Blumenthal
Tony Murgo
Whitney Helms
Jun Yang
Runyan Jin
Jennifer Shen
Rosane Charlab-Orbach

Objectives:

Review the current labeling with the applicant and provide explanations for BI proposals that FDA is not accepting.

Discussion:

The current labeling was reviewed with BI.

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/s/

DEANNE R VARNEY
06/28/2013

Varney, Deanne

From: Varney, Deanne
Sent: Friday, June 28, 2013 3:55 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Labeling

Hi Ann,

Please find attached FDA's fourth round of proposed edits to the afatinib PI and PPI. In addition to these edits, please update the Table of Contents, update table and figure numbers if needed, and correct formatting as needed.

Please review our proposed edits and comments to the afatinib labeling and determine if you are in agreement with the proposed edits. Please accept all edits that you agree with, make any additional edits in track changes, and submit the updated labeling to your NDA by **COB on Monday, July 1, 2013.**

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
06/28/2013

Varney, Deanne

om:	ees_admin@fda.gov
ent:	Wednesday, June 26, 2013 11:07 PM
To:	Varney, Deanne; Godwin, Francis; Martin, Jewell; Zhou, Liang; Hsieh, Li Shan; Salganik, Maria*; Spain, Nancy *; Kyada, Yogesh*
Subject:	Overall OC Recommendation NDA 201292/000 Decision: ACCEPTABLE, Decision Date: 06/26/2013, Re-evaluation Date: 05/03/2014

This is a system generated email message to notify you that the
Overall Compliance Recommendation has been made for the above Application.

For general questions about how to use EES in your work, send
an email to EESQUESTIONS (EESQUESTIONS@cder.fda.gov).
To contact the EES technical staff, send an email to
CDER EES Help (EESHELP@fda.hhs.gov). Thank you.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 201292/000	**Action Goal:**	
Date:	15-NOV-2012	**District Goal:**	15-MAR-2013
Regulatory:	15-JUL-2013		
Applicant:	BOEHRINGER INGELHEIM	**Brand Name:**	Afatinib
	900 RIDGEBURY RD	**Estab. Name:**	
	RIDGEFIELD, CT 06877	**Generic Name:**	Afatinib
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	107	001; TABLET, FILM COATED; AFATINIB; EQ 20MG BASE 002; TABLET, FILM COATED; AFATINIB; EQ 30MG BASE 003; TABLET, FILM COATED; AFATINIB; EQ 40MG BASE (b) (4)	

Application Comment:

FDA Contacts:	L. HSIEH	Prod Qual Reviewer		3017961682
	J. MARTIN	Product Quality PM	(HFV-530)	3017962072
	D. VARNEY	Regulatory Project Mgr	(HFD-107)	3017960297
	L. ZHOU	Team Leader		3017961781

Overall Recommendation:	ACCEPTABLE	on 26-JUN-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 06-FEB-2013	by EES_PROD		
	PENDING	on 07-DEC-2012	by EES_PROD		
	PENDING	on 06-DEC-2012	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: (b) (4)
RESPONSIBILITIES:
TESTING OF TABLETS, INCLUDING STABILITY TESTING (on 07-DEC-2012 by J. MARTIN (HFV-530) 3017962072)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	07-DEC-2012				MARTINJ
SUBMITTED TO DO NME	10-DEC-2012	Product Specific			SHARPT
DO RECOMMENDATION	18-DEC-2012			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	27-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610492 **FEI:** 3002806556

BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG

BINGER STREET 173
INGELHEIM AM RHEIN, RHEINLAND-PFALZ, GERMANY

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

Establishment Comment: COMPLETE ADDRESS LISTED AS: BINGER STRASSE173, 55216 INGELHEIM AM, RHEIN GERMANY,
D-U-N-S: 551147440
SITE RESPONSIBILITIES LISTED AS:MANUFACTURING OF BULK TABLETS,
TESTING OF TABLETS, INCLUDING STABILITY TESTING, TEST ON
(b) (4) DEGRADATION, TESTING OF EXCIPIENTS, PRIMARY PACKAGING AND LABELING, SECONDARY PACKAGING AND LABELING MANUFACTURING, PACKAGING, LABELING, AND ANALYTICAL TESTING INCLUDING STABILITY TESTING
CONTACT EMAIL:
WOLFGANG.WERRA@BEOHRINGERINGELHEIM.COM (on 27-NOV-2012 by J. MARTIN (HFV-530) 3017962072)
RESPONSIBILITIES LISTED AS: MANUFACTURING, PACKAGING, LABELING,AND ANALYTICAL TESTING INCLUDING STABILITY TESTING
D-U-N-S: 551147440
(on 27-NOV-2012 by J. MARTIN (HFV-530) 3017962072)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** POTENTIAL OAI

TABLETS, PROMPT RELEASE POTENTIAL OAI

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	06-DEC-2012				MARTINJ
SUBMITTED TO DO	11-DEC-2012	Product Specific			SHARPT
UNDER REVIEW	12-DEC-2012				PHILPYE
DO RECOMMENDATION	15-APR-2013			WITHHOLD	PHILPYE
				PENDING REGULATORY ACTION WITH	
UNDER REVIEW	05-JUN-2013				PHILPYE
DO RECOMMENDATION	25-JUN-2013			ACCEPTABLE	PHILPYE
AS PER REG DISCRETION REVIEW MEMO. SEE EMAIL/DOCUMENT SENT VIA M. FARBMAN ON 6/25/2013.				BASED ON FILE REVIEW	
OC RECOMMENDATION	26-JUN-2013			ACCEPTABLE	WILLIAMSJU
AS PER REG DISCRETION REVIEW MEMO. SEE EMAIL/DOCUMENT SENT VIA M. FARBMAN ON 6/25/2013.				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	06-DEC-2012				MARTINJ
SUBMITTED TO DO	12-DEC-2012	Product Specific			STOCKM
UNDER REVIEW	18-DEC-2012				PHILPYE
DO RECOMMENDATION	15-APR-2013			WITHHOLD	PHILPYE
				PENDING REGULATORY ACTION WITH	
UNDER REVIEW	05-JUN-2013				PHILPYE

DO RECOMMENDATION	25-JUN-2013	ACCEPTABLE	PHILPYE
AS PER REG DISCRETION REVIEW MEMO. SEE EMAIL/DOCUMENT SENT VIA M. FARBMAN ON 6/25/2013.		BASED ON FILE REVIEW	
OC RECOMMENDATION	26-JUN-2013	ACCEPTABLE	WILLIAMSJU
AS PER REG DISCRETION REVIEW MEMO. SEE EMAIL/DOCUMENT SENT VIA M. FARBMAN ON 6/25/2013.		DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: RESPONSIBILITIES LISTED AS:
TESTING OF TABLETS, INCLUDING STABILITY TESTING, TEST ON (b) (4) DEGRADATION (b) (4) (on 27-NOV-2012 by J. MARTIN (HFV-530) 3017962072)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	06-DEC-2012				MARTINJ
SUBMITTED TO DO	12-DEC-2012	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	18-DEC-2012	Product Specific			PHILPYE
INSPECTION SCHEDULED	19-MAR-2013		30-APR-2013		IRIVERA
DO RECOMMENDATION	13-MAY-2013			ACCEPTABLE	PHILPYE
AS PER M. FARBMAN, ATL				INSPECTION	
OC RECOMMENDATION	13-MAY-2013			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

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/s/

MARY GRACE LUBAO
07/22/2013

WRAP UP MEETING MINUTES
June 10, 2013

New NDA 201292
Gilotrif (afatinib)
Boehringer Ingelheim

Submission Date: November 14, 2012
Received Date: November 15, 2012
PDUFA Date: July 15, 2013

Current Review Team for NDA 201292:
Patricia Keegan, Director DOP2
Deanne Varney, Regulatory Health Project Manager
Karen Jones (CPMS)
Shakun Malik, Medical Officer
Anthony Murgo, Medical Officer (CDTL)
Jonathan Norton, Statistics
Kun He, Statistics (TL)
Runyan Jin, Clinical Pharmacology
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology (TL)
Dubravka Kufrin, Non-Clinical
Whitney Helms, Non-Clinical (TL)
Li Shan Hsieh, Quality
Liang Zhou, Quality (TL)
Ali Al Hakim, Quality (TL)
Jewell Martin, Quality (ONDQA RPM)
Angelica Dorantes, Biopharmaceutics TL
Elsbeth Chikhale, Biopharmaceutics Reviewer
Rosane Charlab Orbach, Genomics Reviewer

Consults for NDA 201292:
James Schlick, OSE Proprietary Name Reviewer and DMEPA Reviewer
Todd Bridges, DMEPA TL
Bob Pratt, DRISK
Cynthia Lacivita, DRISK TL
Kate Coyle, DPV
Corrinne Kulick, DPV TL
Quynh-Van Tran, OPDP Professional Reviewer
Shenee Toombs, OPDP, Consumer Reviewer
Lauren Iacono-Connors, OSI
Tammy Brent-Howard, Maternal Health
Carrie Ceresa, Maternal Health TL
Karen Dowdy, PLT
Barbera Fuller, PLT (TL)
Adel Abou-Ali, DEPI

CDRH Review Team for PMA:
Jennifer Shen

Dates That Signed Reviews Are Due:

	PDUFA Date
CDTL	June 20, 2013
Division Director	July 5, 2013
Office Director	July 15, 2013

Discuss Remaining Outstanding Pre-Action Items:

1. **Target Action Date**

   Discussion: The target action date will be 7/15/13. CDRH is still waiting on information regarding the companion diagnostic, and DIDQ is preparing the final clearance documents. CDER will inform CDRH when CDER is close to ready to take an action.

2. **Labeling:** Currently with BI, counter-proposal expected June 11th

   a. Section 14 forest plots
   b. Review of highlights
   c. Final SRPI review

   Discussion: No further discussion occurred at the meeting.

3. **Signed Review Status:**

   a. Primary Reviews: All complete
   b. Consult Reviews: All complete
   c. Secondary CMC Review: Outstanding
   d. CDTL: Outstanding
   e. Division Director: Outstanding

   Discussion: All outstanding reviews are on track to be completed on time.

4. **PMCs and PMRs**: One PMC to submit the final overall survival analysis from Study 1200.32. Milestone Date: 4/30/2014

   Discussion: The team confirmed that no additional PMCs or PMRs are required.

5. **Postmarket Safety Surveillance**: What adverse events should DPV look for once afatinib is on the market?

   Discussion: The review team does not have any adverse reactions of concern that are not in the PI.

6. **Press Release/ASCO Burst**: In progress

Discussion: An “information alert” will also be released.

7. **Exclusivity Summary –** In progress

   Discussion: No further discussion occurred at the meeting.

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/s/

DEANNE R VARNEY
06/10/2013

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, June 06, 2013 3:33 PM
To: 'ann.agnor@boehringer-ingelheim.com'
Subject: RE: Afatinib NDA 201292 - Labeling Edits

Hi Ann,

Thank you for sending these draft forest plots. We have a couple of comments.

1. Please define NE as "not estimable" in a footnote
2. Please edit the HR values to only have 2 digits after the decimal
3. Please delete the CI's
4. Please include the "n" for each subgroup; this can be placed in the first column next to the subgroup in parentheses

Please let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Wednesday, June 05, 2013 10:21 AM
To: Varney, Deanne
Subject: RE: Afatinib NDA 201292 - Labeling Edits

Hi Deanne,

With regard to the Forest plots included in the last point on the list below, BI would like to propose that the modified Forest Plots, as shown below and in the attachment, are considered for inclusion in the labeling. The FPs are similar to the ones currently in the propose labeling, but include median PFS and OS data, as discussed at the LCM. I know this is being provide very close to the start of the TC, but perhaps it would be very helpful to get FDA's feedback on this at the TC.

(b) (4)

[redacted]

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Varney, Deanne [mailto:Deanne.Varney@fda.hhs.gov]
Sent: Wednesday, June 05, 2013 9:00 AM
To: Agnor,Ann (DRA) BIP-US-R
Subject: RE: Afatinib NDA 201292 - Labeling Edits

Thank you!

An unrelated question – have you submitted the new goal date for your PMC as an amendment to the NDA yet? I don't remember seeing it, so just wanted to follow-up.

Thanks!
Deanne

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Wednesday, June 05, 2013 8:58 AM
To: Varney, Deanne
Subject: RE: Afatinib NDA 201292 - Labeling Edits

Dear Deanne,

Please find below a list of points that BI wishes to discuss at today's TC:

- **In section 5.1,** BI would like to better understand FDA's consideration for not including the information on [redacted] (b) (4), which we believe is meaningful information for the prescriber to be aware of.

- **In section 5.6,** BI accepts the FDA's proposals to changes in the text for this Warning, but would like to better understand the Division's rationale for naming this Warning "Cardiomyopathy" since this severe AE was not seen in the clinical trials.

- **In sections 5.7 and 8.1,** BI would like to better understand FDA's conclusion that there was "no overt toxicity at 5 mg/kg" based on the data provided since we conclude differently.

- **In section 8.1,** BI would like to better understand FDA's conclusion that there was "increased post-implantation loss" based on the data provided since we conclude differently.

- **In section 14,** BI would like to include the median PFS and OS values along with the HRs for the subgroups, as discussed at the LCM (either in the Forest Plots or as text). BI would like to better understand the Division's rationale for not accepting an additional KM curve for the subgroup of the common mutations (Del19 and L858R) considering that this is the indicated patient population and we believe, based on a survey of community oncologists, is necessary for the prescriber to understand the indication clearly.

Thank you and talk to you soon.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Varney, Deanne [mailto:Deanne.Varney@fda.hhs.gov]
Sent: Tuesday, June 04, 2013 9:34 AM
To: Agnor,Ann (DRA) BIP-US-R
Subject: Afatinib NDA 201292 - Labeling Edits

Hello Ann,

Please find attached FDA's third round of proposed edits to the afatinib PI and PPI. In addition to these edits, please update the Table of Contents, update table and figure numbers if needed, and correct formatting as needed.

Please review our proposed edits and comments to the afatinib labeling and determine if you are in agreement with the proposed edits. Please accept all edits that you agree with, make any additional edits in track changes, and submit the updated labeling to your NDA by **COB on Tuesday**, **June 11, 2013**.

In addition, if you could send me a list of the points you would like to discuss during our tcon tomorrow by 9AM tomorrow morning, it would be greatly appreciated.

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
06/06/2013

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, June 05, 2013 1:52 PM
To: 'ann.agnor@boehringer-ingelheim.com'
Subject: RAfatinib NDA 201292 - Labeling Edits

Hi Ann,

Please use this version of labeling during your review. The additional edits were made to Highlights (D&A) and Section 8.7. As stated below, please update the Table of Contents, update table and figure numbers if needed, and correct formatting as needed.

Please review our proposed edits and comments to the afatinib labeling and determine if you are in agreement with the proposed edits. Please accept all edits that you agree with, make any additional edits in track changes, and submit the updated labeling to your NDA by **COB on Tuesday, June 11, 2013.**

Thank you,
Deanne

From: Varney, Deanne
Sent: Tuesday, June 04, 2013 9:34 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Labeling Edits

Hello Ann,

Please find attached FDA's third round of proposed edits to the afatinib PI and PPI. In addition to these edits, please update the Table of Contents, update table and figure numbers if needed, and correct formatting as needed.

Please review our proposed edits and comments to the afatinib labeling and determine if you are in agreement with the proposed edits. Please accept all edits that you agree with, make any additional edits in track changes, and submit the updated labeling to your NDA by **COB on Tuesday, June 11, 2013.**

In addition, if you could send me a list of the points you would like to discuss during our tcon tomorrow by 9AM tomorrow morning, it would be greatly appreciated.

<< File: 20130604_FDA Edits.doc >>
Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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DEANNE R VARNEY
06/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 5, 2013

From: Deanne Varney, RPM, DOP2/OHOP/CDER/FDA

Subject: NDA 201292

TELECONFERNCE

Sponsor Attendees:

Clinical:

Mehdi Shahidi, MD	Leader Clinical Development Afatinib
Dennis O'Brien, MD	Team Member, Drug Safety
Victoria Zazulina, MD	Leader Clinical Development Afatinib NSCLC
Vikram Chand, MD	Team Member Medicine, Oncology
Rainer Kleemann, Dr. med. vet.	International Project Leader

Nonclinical/CMC:

James Segretario, PhD	Director, CMC Regulatory Affairs
Peter Stei, Dr. med. vet.,	Nonclinical Drug Safety

Biometrics & Data Management:

James Love, M. Stat.	Project Statistician

Regulatory:

Ann Agnor, MS	Regulatory Affairs US
Pamela Strode	Executive Director, Regulatory Affairs
David Jones, MD	Regulatory Area Lead, Oncology
Thorsten Laux, PhD	Global Regulatory Affairs Manager
Joanne Palmisano, MD	Vice President, Regulatory Affairs
Terry Keyser	Associate Director, Regulatory Affairs

FDA Attendees:

Deanne Varney
Shakun Malik
Patricia Keegan
Gideon Blumenthal
Tony Murgo
Whitney Helms
Dubravka Kufrin
Jun Yang
Runyan Jin

Jennifer Shen
Reena Phillips
Elizabeth Mansfield
Kate Coyle
Kun He
Rosane Charlab-Orbach

Objectives:

Review the current labeling with the applicant and provide explanations for questions posed by the applicant in regards to the PI.

Discussion:

1. BI requested clarification for naming Section 5.6 "Cardiomyopathy" (b) (4) FDA noted that when a decision is made to include something in the Warnings section, the serious potential outcome must be discussed, and that although the numbers were small, symptomatic patients were seen in early clinical trials. Therefore, prescribers should be alerted that cardiomyopathy is a possibility, and since it is not being monitored for, they must understand the potential severity.

   BI noted that they did not identify cardiomyopathy as a risk for use of afatinib in the pivotal trial, and they would like to indicate what was seen in the trial. FDA reiterated that the concern lies in the larger data set, and that in practice there will be patients who are susceptible to cardiomyopathy, so it needs to be clear in the PI that it is a possibility.

   BI will take this explanation under consideration.

2. BI requested clarification on the Division's rationale (b) (4)) in Section 14 of the PI, considering that this is the indicated patient population. FDA noted that it is OHOP's practice to include (b) (4) KM curve for the primary efficacy analysis in the ITT population. (b) (4)

3. BI stated that they would like to include the median PFS and OS values along with the HRs for the subgroups, as discussed at the LCM, either in the Forest Plots or as text. FDA noted that it is preferred that efficacy results be provided in a graphical format, so a forest plot is preferred over a table, and agreed that the forest plot should include the additional information.

4. BI noted that they conducted a survey of 12 oncologists, in which the oncologists did not understand what the "limitation of use" was intended to convey. FDA noted that providers need to be educated on what a limitation of use conveys, but that there is no latitude on including this in the labeling for afatinib. FDA encouraged BI to review the label for the recently approved Tafinlar (dabrafenib) to see how a limitation of use is worded differently when conveying that something is potentially harmful vs. not adequately studied.

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/s/

DEANNE R VARNEY
06/05/2013

TEAM MEETING MINUTES
June 5, 2013

New NDA 201292
Afatinib
Boehringer Ingelheim

Submission Date: November 14, 2012
Received Date: November 15, 2012
PDUFA Date: July 15, 2013

Proposed Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test

Current Review Team for NDA 201292:
Patricia Keegan, Director DOP2
Deanne Varney, Regulatory Health Project Manager
Karen Jones (CPMS)
Shakun Malik, Medical Officer
Anthony Murgo, Medical Officer (CDTL)
Jonathan Norton, Statistics
Kun He, Statistics (TL)
Runyan Jin, Clinical Pharmacology
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology (TL)
Dubravka Kufrin, Non-Clinical
Whitney Helms, Non-Clinical (TL)
Li Shan Hsieh, Quality
Liang Zhou, Quality (TL)
Ali Al Hakim, Quality (TL)
Jewell Martin, Quality (ONDQA RPM)
Angelica Dorantes, Biopharmaceutics TL
Elsbeth Chikhale, Biopharmaceutics Reviewer
Rosane Charlab Orbach, Genomics Reviewer

Consults for NDA 201292:
James Schlick, OSE Proprietary Name Reviewer and DMEPA Reviewer
Todd Bridges, DMEPA TL
Bob Pratt, DRISK
Cynthia Lacivita, DRISK TL
Kate Coyle, DPV
Corrinne Kulick, DPV TL

Quynh-Van Tran, OPDP Professional Reviewer
Shenee Toombs, OPDP, Consumer Reviewer
Lauren Iacono-Connors, OSI
Tammy Brent-Howard, Maternal Health
Carrie Ceresa, Maternal Health TL
Karen Dowdy, PLT
Barbera Fuller, PLT (TL)
Adel Abou-Ali, DEPI

CDRH Review Team for PMA:
Jennifer Shen

Review Status:

- Priority Review requested (PDUFA V --- 8 month review)
- Categorical Exclusion from environmental assessment requested
- Orphan designation granted; exempt from PREA
- Requested waiver of half-page Highlights
- The clinical development of afatinib has been conducted under INDs 67969 and 114002.

Agenda Items:

1. Discuss Target Action Date and CDRH Review Status

Discussion: CDRH noted that a 7/15/13 action date should be feasible.

2. Press Release and ASCO Burst:

Discussion: Information for press release to OPA by 6/14. Start drafting ASCO burst by mid-June

3. Update from Office of Compliance on BI's Response to Warning Letter

Discussion: OC has done a preliminary review of BI's response to the warning letter, and believes the response is such that OC will be able to make an acceptable recommendation for this application. EES will be updated relatively soon.

4. Milestone Goals Remaining:

Milestone	8 month review July 15, 2013
Acknowledgment Letter	November 29, 2012 ***Issued November 20, 2012***
Priority Review Determination/Filing Issues	January 14, 2013

Identified Letter	***Issued January 11, 2013***
Mid-Cycle Communication	February 28, 2013 ***Scheduled February 20, 2013***
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	April 19, 2013
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	April 26, 2013
Issue Discipline Review Letters	April 26, 2013
Late Cycle Meeting	May 7, 2013 *(Briefing package due 4/25/13)*
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 April 22, 2013 April 25, 2013 June 20, 2013 July 5, 2013 July 15, 2013
Compile and circulate Action Letter and Action Package	June 25, 2013
FINAL Action Letter Due	**July 15, 2013**

5. **Review Issues/Updates:**

   a. **Clinical:** None

   b. **Statistical:** None

   c. **Genomics:** None

   d. **Nonclinical:** None

   e. **Clinical Pharmacology:** None

   f. **CMC/Biopharm:** None

   g. **CDRH:** None

6. **Inspections:** See update from Office of Compliance under Item 3.

7. **PMC:** Submit the data from the final overall survival analysis from Study 1200.32 in order to better characterize the effects of afatinib treatment on overall survival.

   PMC Milestone Date:
   Final Submission of complete clinical trial report: 4/30/2014

8. Upcoming Internal Team Meetings:

i. **Labeling Meetings:** As needed

ii. **Remaining Monthly Team Meetings:** July 3, 1013

iii. **Wrap- Up Meeting**: June 10, 2013

8. ODAC Not Needed

9. Consults/Collaborative Reviewers:

OPDP	Quynh-Van Tran - professional reviewer Shenee Toombs - consumer reviewer Olga Salis – RPM
OSE	Sue Kang - OSE RPM Sean Bradley - OSE RPM TL *DMEPA to review carton/container and proprietary name review (request received 11/27/12) – James Schlick Todd Bridges – DMEPA TL DEPI: Adel Abou-Ali DRISK: Bob Pratt/Cynthia LaCivita DPV: Kate Coyle/ Corrinne Kulick
Maternal Health	Tammie Brent-Howard - Reviewer Carrie Ceresa – TL Melissa Tassinari
Facility/OMPQ	The sites have been entered in EES.
OSI	Lauren Iacono-Connors assigned, site selection in progress
Pediatric Page/PeRC	Full Waiver Requested Orphan Designation Granted – exempt from PREA
Patient Labeling Team	Karen Dowdy – Reviewer Barbara Fuller - TL
SEALD	*Consult sent 11/21/12*
QT-IRT	*Consult sent 12/3/12*
SGE's or Patient Representatives	Complete

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/s/

DEANNE R VARNEY
06/05/2013

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, June 04, 2013 9:34 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Labeling Edits

Hello Ann,

Please find attached FDA's third round of proposed edits to the afatinib PI and PPI. In addition to these edits, please update the Table of Contents, update table and figure numbers if needed, and correct formatting as needed.

Please review our proposed edits and comments to the afatinib labeling and determine if you are in agreement with the proposed edits. Please accept all edits that you agree with, make any additional edits in track changes, and submit the updated labeling to your NDA by **COB on Tuesday, June 11, 2013.**

In addition, if you could send me a list of the points you would like to discuss during our tcon tomorrow by 9AM tomorrow morning, it would be greatly appreciated.

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
06/04/2013

Varney, Deanne

From: Malik, Shakun
Sent: Monday, June 03, 2013 3:10 PM
To: dennis.obrien@boehringer-ingelheim.com
Cc: ann.agnor@boehringer-ingelheim.com; james.love@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: Afatinib NDA 201292 - comment to ILD warning in labeling

Dear Dennis,
The label proposes that Grade (b) (4) palmar-plantar erythrodysesthesia syndrome occurred in (b) % of cases. Please clarify in which population?
Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Tuesday, May 21, 2013 3:38 PM
To: Varney, Deanne; Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com
Subject: Re: Afatinib NDA 201292 - comment to ILD warning in labeling

Hi Deanne,

Thank you for letting me know this. Since our counter proposals for this second round are basically complete at this point, do you think it would be beneficial for BI to submit them as planned on May 23, and then perhaps request a TC for next week to discuss the ILD warning - and perhaps other areas where there may not be 100% agreement yet?

Kind regards,
Ann Agnor
BIBI

Sent via AT&T BlackBerry Wireless

From: Varney, Deanne [mailto:Deanne.Varney@fda.hhs.gov]
Sent: Tuesday, May 21, 2013 02:20 PM Eastern Standard Time
To: Agnor,Ann (DRA) BIP-US-R; Malik, Shakun <Shakuntala.Malik@fda.hhs.gov>
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R
Subject: RE: Afatinib NDA 201292 - comment to ILD warning in labeling

Hi Ann,

Dr. Malik is out of the office this week, so a response will need to wait until her return. We can extend the due date for your counter-proposal until Wednesday, May 29th, to allow for resolution of this issue if you would like.

Thank you,
Deanne

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Tuesday, May 21, 2013 1:03 PM
To: Varney, Deanne; Malik, Shakun

Cc: dennis.obrien@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - comment to ILD warning in labeling

Dear Deanne, Dear Dr. Malik,

In the latest round of labeling comments received from FDA, the following comment (in yellow) was noted by FDA with regard to ILD and ILD-like events in the Highlights section:

• Interstitial lung disease (ILD): Occurs in 1.5% of patients. Withhold GILOTRIF for acute onset or worsening of pulmonary symptoms. Discontinue GILOTRIF if ILD is diagnosed. (2.3, 5.3) FDA Comment: Based on the narratives provided and associated symptoms/co-morbities it is not clear what cases were not drug related.

The following is what we are considering to submit on May 23 in response to FDA's labeling comments, with changes noted in red:

5.3 Interstitial Lung Disease (ILD)
ILD or ILD-like (b) (4) ~~adverse reactions~~ (e.g., lung infiltration, pneumonitis, acute respiratory distress syndrome, or alveolitis allergic) occurred in 1.5% of the 3865 patients who received GILOTRIF across clinical trials. (b) (4) The incidence of ILD (b) (4) appeared to be higher in patients of Asian ethnicity (2.1%) as compared to non-Asians (1.2%). The incidence of Grade ≥3 ILD (b) (4) was 1.3% and resulted in death in (b) (4) patients. Withhold GILOTRIF during evaluation of patients with suspected ILD, and discontinue GILOTRIF in patients with confirmed ILD *[see Dosage and Administration (2.3)]*.

BI believes that our proposal reflects our data accurately in terms of events v. reactions. If our proposal is not acceptable, we would appreciate a quick TC to discuss our rationale and address FDA's above comment. Thank you.

Kind regards,
Ann

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

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/s/

DEANNE R VARNEY
06/04/2013

Varney, Deanne

From: Malik, Shakun
Sent: Wednesday, May 29, 2013 11:57 AM
To: dennis.obrien@boehringer-ingelheim.com
Cc: ann.agnor@boehringer-ingelheim.com; james.love@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: NDA 201292 - afatinib request

Please clarify the following in PI:

[redacted] (b) (4)

How many of these trials had periodic monitoring of LVEF?
If not noted by monitoring, how were these patients diagnosed with decrease in LVEF and if by symptoms only, how many needed discontinuation.
Thanks
Shakun

From: dennis.obrien@boehringer-ingelheim.com [mailto:dennis.obrien@boehringer-ingelheim.com]
Sent: Wednesday, May 29, 2013 9:38 AM
To: Malik, Shakun
Cc: ann.agnor@boehringer-ingelheim.com; james.love@boehringer-ingelheim.com
Subject: NDA 201292 - afatinib request

Good morning Shakun
When you look at the frequency of grade 3 diarrhea in those with a Cockroft-Gault CrCl < 60, versus those >=60 in study 1, the numbers remain essentially unchanged from the analysis in the ISS, which used a cutoff of <50. Grade 3 diarrhea was 24.5% among 53 patients with <60 versus 11.9% for patients with >=60. On the other hand, Grade 3 diarrhea was 24.1% among 29 patients with <50 versus 13.5% for patients with >=50. So the association remains between lower baseline renal function and higher rate of grade 3 diarrhea, regardless of whether a cutoff of <50 or <60 is used.

By the way, I noticed an error in a previous email were I stated “29 afatinib treated patients had a baseline CrCl < 60 as calculated from serum Cr”, and I meant to say 29 had a Cr cl” < 50”. This was quoted from the ISS data.

Regards,
Dennis

Boehringer Ingelheim

Dennis O’Brien, MD
Medical Director, Global Safety Evaluations, Oncology
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT
P: 203 791 6466:: [redacted] (b) (6)
dennis.obrien@boehringer-ingelheim.com

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEANNE R VARNEY
05/29/2013

Varney, Deanne

From: Malik, Shakun
Sent: Tuesday, May 28, 2013 1:23 PM
To: dennis.obrien@boehringer-ingelheim.com
Cc: james.love@boehringer-ingelheim.com; ann.agnor@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: NDA 201292 - afatinib request

Dear Ann and Dennis,
Please clarify:
The protocol exclusion for study 1 was Creatinine clearance < 60 ml / min or serum creatinine > 1.5 times upper limit of normal.
The patients with grade 3 diarrhea who had cr clearance <50 was a later event?
Shakun

From: dennis.obrien@boehringer-ingelheim.com [mailto:dennis.obrien@boehringer-ingelheim.com]
Sent: Wednesday, May 01, 2013 5:46 PM
To: Malik, Shakun
Cc: james.love@boehringer-ingelheim.com; ann.agnor@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: NDA 201292 - afatinib request

Dr. Malik,
Yes there is consistency:
For grade 3 diarrhea in SAF 1: for female patients and those with renal impairment the correlation exists. (See attached: ISS Table 2.8.1.15)
For grade 3 rash in SAF 1: for female, low body weight, and mild to moderate renal impairment as there is a 5-6% percentage increase in rate of grade 3 events . (See attached: ISS Table 2.8.4.11)

From SAF to SAF there is variability in what is seen in the risk factor analysis. We included gender, body weight and renal dysfunction as risk factors in the proposed label because of the observed consistency across SAFs and target events.

Regards,

Dennis

Boehringer Ingelheim

Dennis O'Brien, MD
Medical Director, Global Safety Evaluations, Oncology
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT
P: 203 791 6466:: (b) (6)
dennis.obrien@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, May 01, 2013 5:20 PM
To: O'Brien,Dr.,Dennis (DSI) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

OK thanks. Just wanted to confirm. However did you see any correlation with gender, weight and renal dysfunction with these AE's in SAF 1?
Thanks again

From: dennis.obrien@boehringer-ingelheim.com [mailto:dennis.obrien@boehringer-ingelheim.com]
Sent: Wednesday, May 01, 2013 5:18 PM
To: Malik, Shakun; ann.agnor@boehringer-ingelheim.com
Cc: Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik
We utilized SAF-5 for risk factor analyses for rare events i.e. ILD, heart failure, hepatic impairment. For other more common AE, the numbers of events were sufficient to perform risk factor analyses without resorting to SAF-5, which included a potentially confounding mixture or regimens, dosages, and baseline conditions that would not be directly relevant to the intended indication.

Regards,
Dennis

Boehringer Ingelheim

Dennis O'Brien, MD
Medical Director, Global Safety Evaluations, Oncology
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT
P: 203 791 6466:: (b) (6)
dennis.obrien@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, May 01, 2013 5:04 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Did you conduct any such analysis when pooling all patients SAF 5 ?

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Wednesday, May 01, 2013 2:59 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

The analysis of risk factors was based on pooled 50 mg starting dose data (SAF-4) and pooled 40 mg starting dose data (SAF-2) to increase the population size at each starting dose. As proposed in the label, Risk Factor Analysis for experiencing a higher grade EGFR-inhibition mediated event (e.g. diarrhea, rash/acne) shows the highest odds ratio (OR) for female patients, patients with lower body weight, and those with underlying renal impairment. The conclusion was most evident from the analysis from the pooled 50 mg dose as presented in the Summary of Clinical Safety for diarrhea (Module 2.7.4, section 2.1.12.1.4, Table 2.1.12.1.4:2, p 166). However, a similar trend was seen in the 40 mg starting dose, although not as robust (Module 2.7.4, section 2.1.12.1.4, Table 2.1.12.1.4:1, p 165). Analysis from SAF-4 and SAF-2 for rash/acne is also presented (Module 2.7.4, section 2.1.12.2.2, Table 2.1.12.2.2:1, p 172).

I hope this addresses your request but please let me know if you have further questions.

Thank you.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, May 01, 2013 12:13 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Ann,

(b) (4)

[redacted]

Do we have a data on this? Was there any type of such analysis done with SAF 5 or Study 1200.32.?
Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Tuesday, April 30, 2013 4:00 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

I have attached a table with pdfs with the narratives for the ILD-like events in SAF-5, for the 59 cases identified from the broad ILD SMQ. These narratives were previously submitted in the NDA by trial, but are provided in this way for ease of review.

Kind regards,
Ann

From: Agnor,Ann (DRA) BIP-US-R
Sent: Tuesday, April 30, 2013 9:43 AM
To: 'Malik, Shakun'
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Narratives for ILD/ILD-like events were provided in the NDA for all afatinib trials. These narratives were submitted in the form of a single pdf document per applicable trial. So they are currently organized by trial, not by event. For ease of review, we are looking into the possibility to generate consolidated narratives for the SMQ for ILD from the original data lock point of February 9, 2012. I will get back to you on the timeframe for this if it is possible.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Tuesday, April 30, 2013 8:11 AM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Thanks Ann.

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Monday, April 29, 2013 9:18 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

I will get back to you as soon as possible on this… Augmented narratives were submitted in the NDA in the form of a single pdf document per applicable trial, based on the definition agreed upon at the pre-NDA meeting (as below). I will confirm narratives as per your request with my colleagues tomorrow morning.

For studies 1200.32, 1200.22, 1200.23, and 1200.42:
FDA clarified that the sponsor should provide narratives for all deaths attributed to an adverse event in any study arm on the NSCLC trials. It is not necessary to provide narratives for deaths attributed to progressive disease. However, these should be available upon request. Narratives for adverse events leading to discontinuation and serious adverse events should be provided for events which are at least possibly attributable to study drug.

For other studies:
Narratives should be provided for 1) Interstitial lung disease like events; 2) Decreased LVEF/Heart Failure events; 3) Hepatic Failure events for patients on afatinib.

Kind regards,
Ann

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Monday, April 29, 2013 9:09 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Ann,
In SAF-5, 59 cases were identified from the broad ILD SMQ, 28 cases were considered related to the study drug and 31 cases were considered not related to the study drug. In addition to the brief narration given in the ISS of these 31 patients, Are there additional narratives that have been submitted to the NDA?
Thank you
shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Thursday, April 18, 2013 6:39 AM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Here is the requested information on the 5 patients in Study 1200.32 who received 50 mg as a starting dose instead of 40 mg:

Pt 4101010: Had 28 days of afatinib 50 mg before being dose reduced to 40 mg due to a G2 rash.
Pt 4202004: Had 18 days of afatinib 50 mg before discontinuing due to G3 diarrhoea.
Pt 4310003: Is continuing on afatinib 50 mg after 3 years of exposure.
Pt 4807004: Had 12 days of afatinib 50 mg before being dose reduced due to G3 rash.
Pt 5604001: Had 64 days of afatinib 50 mg before being dose reduced due to G1 rash.

Kind regards,
Ann

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, April 17, 2013 5:04 PM

To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Thanks

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Wednesday, April 17, 2013 5:04 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Apologies that I read your message late today as I was out of the office. I will get an answer for you as soon as possible.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, April 17, 2013 4:22 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Ann a quick question
Altogether 21 patients received 50 mg afatinib. Of those, 16 patients had been dose-escalated according to protocol; the remaining 5 patients erroneously received an afatinib starting dose of 50 mg instead of 40 mg.
Were these 5 patients deescalated to 40 mg dose?
How long were they on 50 mg dose?
Thanks
Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Friday, April 05, 2013 2:40 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

We can confirm what you stated below is correct, as shown in Listing 96.1: The mutation sub-types of the 4/23 afatinib-treated patients achieving PR is correct (L858R+T790M; G719X; L858R+S768I; and S768I). None achieved a CR, with 3 being not evaluable.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Friday, April 05, 2013 1:50 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Thanks.
Please confirm the following
of 23 evaluable patients in Afatinib arm, none achieved a complete response, and four achieved a confirmed partial response 1 in each.
L858R and T790M, G719X, L858R+S768I and S768I

Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Friday, April 05, 2013 7:41 AM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Please find attached Table 96.1 “Confirmed and unconfirmed responses with durations (Investigator assessment) for patients with uncommon mutations”. This table includes the unconfirmed and confirmed response data for the 37 patients in Study 1200.32 with an uncommon mutation(s).

Please note that at the time of the primary snapshot, all but 5 of the 37 patients with uncommon mutations had completed their imaging so their tumor response data will not change. Of these 5 patients, 2 were continuing imaging at the time of the OS update.

Patients ongoing at primary snapshot but complete at OS update:

3214009 (Chemo): PD by independent review at primary analysis (13.8 months), PD at OS update by investigator (19.2 months).
3219004 (Chemo): SD by independent review/investigator at primary analysis, PD at OS update by investigator (24.8 months).
5302005 (Afatinib): PD by independent review at primary analysis (11.0 months), PD at OS update by investigator (20.8 months).

Patients ongoing at OS update:

3601024: (Afatinib): PR by independent review/investigator at primary analysis, still PR by investigator at OS update.
3603008: (Afatinib): PR by independent review/investigator at primary analysis, still PR by investigator at OS update.

In summary, new independent data will provide an update on tumor response for 3 patients (3219004, 3601024 and 3603008).

I hope this address you request ,but please let me know if you need further information/clarification.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Thursday, April 04, 2013 3:10 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

That is OK. Thank you again

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Thursday, April 04, 2013 3:05 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

We would like to have the trial statistician for Study 1200.32 confirm the results we will provide in response to the below request before sending to you. As he is located in the UK, we would like to wait until tomorrow morning before responding (due to the time difference). I regret the delay but hope this is okay.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Thursday, April 04, 2013 1:47 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Also please indicate

- if the response rates provided are confirmed(i.e. f/up scan after 30days) and
- Duration of response

Shakun

From: Malik, Shakun
Sent: Thursday, April 04, 2013 1:10 PM
To: 'ann.agnor@boehringer-ingelheim.com'
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Ann and Jim,

In RESPONSE TO REQUEST FOR INFORMATION – STUDY 1200.32 UPDATED Provided on January 28, table 4 2013 you provided a table (table 4) as investigator assessments of overall survival and other efficacy results for patients within the "Other" EGFR mutation because independent assessments have not been updated for the January 2013 database. Please provide us with updated data as per IRR.

Thank you
Shakun

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEANNE R VARNEY
05/28/2013

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, May 16, 2013 8:56 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Labeling Edits

Hello Ann,

Please find attached FDA's second round of proposed edits to the afatinib PI and PPI. In addition to these edits, please update table and figure numbers, and correct formatting as needed.

Please review our proposed edits and comments to the afatinib labeling and determine if you are in agreement with the proposed edits. Please accept all edits that you agree with, make any additional edits in track changes, and submit the updated labeling to your NDA by **Thursday, May 23, 2013**. Please also include in the submitted PI your proposed forest plot including data for the common mutations, including medians.

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEANNE R VARNEY
05/16/2013

Varney, Deanne

From: Malik, Shakun
Sent: Friday, May 03, 2013 4:56 PM
To: dennis.obrien@boehringer-ingelheim.com
Cc: james.love@boehringer-ingelheim.com; ann.agnor@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: NDA 201292 - afatinib request

Dear Dennis,

Please confirm that these numbers are correct. In study 1

1) The incidence of Grade 3 Rash appeared to be higher in females as compared to males 18% vs. 12% and in patients with body weight (<50kg) compared patients with body weight (>50kg) 15% vs. 20%.
2) The incidence of Grade 3 Diarrhea appeared be higher in females as compared to males 19% vs.7% and in patients with body weight (<50kg) compared patients with body weight (>50kg) 14% vs. 18%.

This trend of increase seems to be in elderly also. Your thoughts?

The renal impairment and grade 3 does not make sense as it seems that moderate have more % than mild? And more in moderate than normal for diarrhea

Is there a similar variables trend in overall toxicity % in SAF 1 ?

Thank you for your help

shakun

From: dennis.obrien@boehringer-ingelheim.com [mailto:dennis.obrien@boehringer-ingelheim.com]
Sent: Wednesday, May 01, 2013 5:46 PM
To: Malik, Shakun
Cc: james.love@boehringer-ingelheim.com; ann.agnor@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: NDA 201292 - afatinib request

Dr. Malik,
Yes there is consistency:
For grade 3 diarrhea in SAF 1: for female patients and those with renal impairment the correlation exists. (See attached: ISS Table 2.8.1.15)
For grade 3 rash in SAF 1: for female, low body weight, and mild to moderate renal impairment as there is a 5-6% percentage increase in rate of grade 3 events . (See attached: ISS Table 2.8.4.11)

From SAF to SAF there is variability in what is seen in the risk factor analysis. We included gender, body weight and renal dysfunction as risk factors in the proposed label because of the observed consistency across SAFs and target events.

Regards,

Dennis

Dennis O'Brien, MD
Medical Director, Global Safety Evaluations, Oncology
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT
P: 203 791 6466:: (b) (6)
dennis.obrien@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, May 01, 2013 5:20 PM
To: O'Brien,Dr.,Dennis (DSI) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

OK thanks. Just wanted to confirm. However did you see any correlation with gender, weight and renal dysfunction with these AE's in SAF 1?
Thanks again

From: dennis.obrien@boehringer-ingelheim.com [mailto:dennis.obrien@boehringer-ingelheim.com]
Sent: Wednesday, May 01, 2013 5:18 PM
To: Malik, Shakun; ann.agnor@boehringer-ingelheim.com
Cc: Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik
We utilized SAF-5 for risk factor analyses for rare events i.e. ILD, heart failure, hepatic impairment. For other more common AE, the numbers of events were sufficient to perform risk factor analyses without resorting to SAF-5, which included a potentially confounding mixture or regimens, dosages, and baseline conditions that would not be directly relevant to the intended indication.

Regards,
Dennis

Dennis O'Brien, MD
Medical Director, Global Safety Evaluations, Oncology
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT
P: 203 791 6466:: (b) (6)
dennis.obrien@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, May 01, 2013 5:04 PM
To: Agnor,Ann (DRA) BIP-US-R

Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Did you conduct any such analysis when pooling all patients SAF 5 ?

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Wednesday, May 01, 2013 2:59 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

The analysis of risk factors was based on pooled 50 mg starting dose data (SAF-4) and pooled 40 mg starting dose data (SAF-2) to increase the population size at each starting dose. (b) (4) [redacted] The conclusion was most evident from the analysis from the pooled 50 mg dose as presented in the Summary of Clinical Safety for diarrhea (Module 2.7.4, section 2.1.12.1.4, Table 2.1.12.1.4:2, p 166). However, a similar trend was seen in the 40 mg starting dose, although not as robust (Module 2.7.4, section 2.1.12.1.4, Table 2.1.12.1.4:1, p 165). Analysis from SAF-4 and SAF-2 for rash/acne is also presented (Module 2.7.4, section 2.1.12.2.2, Table 2.1.12.2.2:1, p 172).

I hope this addresses your request but please let me know if you have further questions.

Thank you.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, May 01, 2013 12:13 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Ann,
You want to add the following to the label

(b) (4) [redacted]

Do we have a data on this? Was there any type of such analysis done with SAF 5 or Study 1200.32.?
Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Tuesday, April 30, 2013 4:00 PM
To: Malik, Shakun

Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

I have attached a table with pdfs with the narratives for the ILD-like events in SAF-5, for the 59 cases identified from the broad ILD SMQ. These narratives were previously submitted in the NDA by trial, but are provided in this way for ease of review.

Kind regards,
Ann

From: Agnor,Ann (DRA) BIP-US-R
Sent: Tuesday, April 30, 2013 9:43 AM
To: 'Malik, Shakun'
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Narratives for ILD/ILD-like events were provided in the NDA for all afatinib trials. These narratives were submitted in the form of a single pdf document per applicable trial. So they are currently organized by trial, not by event. For ease of review, we are looking into the possibility to generate consolidated narratives for the SMQ for ILD from the original data lock point of February 9, 2012. I will get back to you on the timeframe for this if it is possible.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Tuesday, April 30, 2013 8:11 AM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Thanks Ann.

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Monday, April 29, 2013 9:18 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

I will get back to you as soon as possible on this… Augmented narratives were submitted in the NDA in the form of a single pdf document per applicable trial, based on the definition agreed upon at the pre-NDA meeting (as below). I will confirm narratives as per your request with my colleagues tomorrow morning.

For studies 1200.32, 1200.22, 1200.23, and 1200.42:
FDA clarified that the sponsor should provide narratives for all deaths attributed to an adverse event in any study arm on the NSCLC trials. It is not necessary to provide

narratives for deaths attributed to progressive disease. However, these should be available upon request. Narratives for adverse events leading to discontinuation and serious adverse events should be provided for events which are at least possibly attributable to study drug.

For other studies:
Narratives should be provided for 1) Interstitial lung disease like events; 2) Decreased LVEF/Heart Failure events; 3) Hepatic Failure events for patients on afatinib.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

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Sent: Monday, April 29, 2013 9:09 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Ann,
In SAF-5, 59 cases were identified from the broad ILD SMQ, 28 cases were considered related to the study drug and 31 cases were considered not related to the study drug. In addition to the brief narration given in the ISS of these 31 patients, Are there additional narratives that have been submitted to the NDA?
Thank you
shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Thursday, April 18, 2013 6:39 AM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Here is the requested information on the 5 patients in Study 1200.32 who received 50 mg as a starting dose instead of 40 mg:

Pt 4101010: Had 28 days of afatinib 50 mg before being dose reduced to 40 mg due to a G2 rash.
Pt 4202004: Had 18 days of afatinib 50 mg before discontinuing due to G3 diarrhoea.
Pt 4310003: Is continuing on afatinib 50 mg after 3 years of exposure.
Pt 4807004: Had 12 days of afatinib 50 mg before being dose reduced due to G3 rash.
Pt 5604001: Had 64 days of afatinib 50 mg before being dose reduced due to G1 rash.

Kind regards,
Ann

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From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, April 17, 2013 5:04 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Thanks

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Sent: Wednesday, April 17, 2013 5:04 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Apologies that I read your message late today as I was out of the office. I will get an answer for you as soon as possible.

Kind regards,
Ann

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
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Sent: Wednesday, April 17, 2013 4:22 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Ann a quick question
Altogether 21 patients received 50 mg afatinib. Of those, 16 patients had been dose-escalated according to protocol; the remaining 5 patients erroneously received an afatinib starting dose of 50 mg instead of 40 mg.
Were these 5 patients deescalated to 40 mg dose?
How long were they on 50 mg dose?
Thanks
Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Friday, April 05, 2013 2:40 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

We can confirm what you stated below is correct, as shown in Listing 96.1: The mutation sub-types of the 4/23 afatinib-treated patients achieving PR is correct (L858R+T790M; G719X; L858R+S768I; and S768I). None achieved a CR, with 3 being not evaluable.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Friday, April 05, 2013 1:50 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Thanks.
Please confirm the following
of 23 evaluable patients in Afatinib arm, none achieved a complete response, and four achieved a confirmed partial response 1 in each.
L858R and T790M, G719X, L858R+S768I and S768I

Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Friday, April 05, 2013 7:41 AM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Please find attached Table 96.1 “Confirmed and unconfirmed responses with durations (Investigator assessment) for patients with uncommon mutations”. This table includes the unconfirmed and confirmed response data for the 37 patients in Study 1200.32 with an uncommon mutation(s).

Please note that at the time of the primary snapshot, all but 5 of the 37 patients with uncommon mutations had completed their imaging so their tumor response data will not change. Of these 5 patients, 2 were continuing imaging at the time of the OS update.

Patients ongoing at primary snapshot but complete at OS update:

3214009 (Chemo): PD by independent review at primary analysis (13.8 months), PD at OS update by investigator (19.2 months).

3219004 (Chemo): SD by independent review/investigator at primary analysis, PD at OS update by investigator (24.8 months).
5302005 (Afatinib): PD by independent review at primary analysis (11.0 months), PD at OS update by investigator (20.8 months).

Patients ongoing at OS update:

3601024: (Afatinib): PR by independent review/investigator at primary analysis, still PR by investigator at OS update.
3603008: (Afatinib): PR by independent review/investigator at primary analysis, still PR by investigator at OS update.

In summary, new independent data will provide an update on tumor response for 3 patients (3219004, 3601024 and 3603008).

I hope this address you request ,but please let me know if you need further information/clarification.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Thursday, April 04, 2013 3:10 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

That is OK. Thank you again

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Thursday, April 04, 2013 3:05 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

We would like to have the trial statistician for Study 1200.32 confirm the results we will provide in response to the below request before sending to you. As he is located in the UK, we would like to wait until tomorrow morning before responding (due to the time difference). I regret the delay but hope this is okay.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Thursday, April 04, 2013 1:47 PM

To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Also please indicate

- if the response rates provided are confirmed(i.e. f/up scan after 30days) and
- Duration of response

Shakun

From: Malik, Shakun
Sent: Thursday, April 04, 2013 1:10 PM
To: 'ann.agnor@boehringer-ingelheim.com'
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Ann and Jim,

In RESPONSE TO REQUEST FOR INFORMATION – STUDY 1200.32 UPDATED Provided on January 28, table 4 2013 you provided a table (table 4) as investigator assessments of overall survival and other efficacy results for patients within the "Other" EGFR mutation because independent assessments have not been updated for the January 2013 database. Please provide us with updated data as per IRR.

Thank you
Shakun

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEANNE R VARNEY
05/06/2013

Varney, Deanne

From: Malik, Shakun
Sent: Thursday, May 02, 2013 4:17 PM
To: dennis.obrien@boehringer-ingelheim.com
Cc: james.love@boehringer-ingelheim.com; ann.agnor@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: NDA 201292 - afatinib request

Dennis and Ann,
Some clarifications

1) In the revised label you state that [redacted (b) (4)] . Is this different than the expanded access program that the FDA approved?
2) ILD was noted more in Asian population. What was the % of ILD noted in this population in SAF 5(related or unrelated) .

Thanks

From: dennis.obrien@boehringer-ingelheim.com [mailto:dennis.obrien@boehringer-ingelheim.com]
Sent: Wednesday, May 01, 2013 5:46 PM
To: Malik, Shakun
Cc: james.love@boehringer-ingelheim.com; ann.agnor@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: NDA 201292 - afatinib request

Dr. Malik,
Yes there is consistency:
For grade 3 diarrhea in SAF 1: for female patients and those with renal impairment the correlation exists. (See attached: ISS Table 2.8.1.15)
For grade 3 rash in SAF 1: for female, low body weight, and mild to moderate renal impairment as there is a 5-6% percentage increase in rate of grade 3 events . (See attached: ISS Table 2.8.4.11)

From SAF to SAF there is variability in what is seen in the risk factor analysis. We [redacted (b) (4)] observed consistency across SAFs and target events.

Regards,

Dennis

Boehringer Ingelheim

Dennis O'Brien, MD
Medical Director, Global Safety Evaluations, Oncology
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT
P: 203 791 6466:: [redacted (b) (6)]
dennis.obrien@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, May 01, 2013 5:20 PM
To: O'Brien,Dr.,Dennis (DSI) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

OK thanks. Just wanted to confirm. However did you see any correlation with gender, weight and renal dysfunction with these AE's in SAF 1?
Thanks again

From: dennis.obrien@boehringer-ingelheim.com [mailto:dennis.obrien@boehringer-ingelheim.com]
Sent: Wednesday, May 01, 2013 5:18 PM
To: Malik, Shakun; ann.agnor@boehringer-ingelheim.com
Cc: Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik
We utilized SAF-5 for risk factor analyses for rare events i.e. ILD, heart failure, hepatic impairment. For other more common AE, the numbers of events were sufficient to perform risk factor analyses without resorting to SAF-5, which included a potentially confounding mixture or regimens, dosages, and baseline conditions that would not be directly relevant to the intended indication.

Regards,
Dennis

Boehringer Ingelheim

Dennis O'Brien, MD
Medical Director, Global Safety Evaluations, Oncology
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT
P: 203 791 6466:: (b) (6)
dennis.obrien@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, May 01, 2013 5:04 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Did you conduct any such analysis when pooling all patients SAF 5 ?

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Wednesday, May 01, 2013 2:59 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

The analysis of risk factors was based on pooled 50 mg starting dose data (SAF-4) and pooled 40 mg starting dose data (SAF-2) to increase the population size at each starting dose. (b) (4) [redacted] The conclusion was most evident from the analysis from the pooled 50 mg dose as presented in the Summary of Clinical Safety for diarrhea (Module 2.7.4, section 2.1.12.1.4, Table 2.1.12.1.4:2, p 166). However, a similar trend was seen in the 40 mg starting dose, although not as robust (Module 2.7.4, section 2.1.12.1.4, Table 2.1.12.1.4:1, p 165). Analysis from SAF-4 and SAF-2 for rash/acne is also presented (Module 2.7.4, section 2.1.12.2.2, Table 2.1.12.2.2:1, p 172).

I hope this addresses your request but please let me know if you have further questions.

Thank you.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, May 01, 2013 12:13 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Ann,

(b) (4) [redacted]

Do we have a data on this? Was there any type of such analysis done with SAF 5 or Study 1200.32.?
Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Tuesday, April 30, 2013 4:00 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

I have attached a table with pdfs with the narratives for the ILD-like events in SAF-5, for the 59 cases identified from the broad ILD SMQ. These narratives were previously submitted in the NDA by trial, but are provided in this way for ease of review.

Kind regards,
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FDA clarified that the sponsor should provide narratives for all deaths attributed to an adverse event in any study arm on the NSCLC trials. It is not necessary to provide narratives for deaths attributed to progressive disease. However, these should be available upon request. Narratives for adverse events leading to discontinuation and serious adverse events should be provided for events which are at least possibly attributable to study drug.

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shakun

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Pt 4807004: Had 12 days of afatinib 50 mg before being dose reduced due to G3 rash.
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Subject: RE: NDA 201292 - afatinib request

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Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Apologies that I read your message late today as I was out of the office. I will get an answer for you as soon as possible.

Kind regards,
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Boehringer Ingelheim

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Ann a quick question
Altogether 21 patients received 50 mg afatinib. Of those, 16 patients had been dose-escalated according to protocol; the remaining 5 patients erroneously received an afatinib starting dose of 50 mg instead of 40 mg.
Were these 5 patients deescalated to 40 mg dose?
How long were they on 50 mg dose?
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Sent: Friday, April 05, 2013 2:40 PM
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Dear Dr. Malik,

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Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

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Please confirm the following
of 23 evaluable patients in Afatinib arm, none achieved a complete response, and four achieved a confirmed partial response 1 in each.
L858R and T790M, G719X, L858R+S768I and S768I

Shakun

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Sent: Friday, April 05, 2013 7:41 AM
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Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Please find attached Table 96.1 “Confirmed and unconfirmed responses with durations (Investigator assessment) for patients with uncommon mutations”. This table includes the unconfirmed and confirmed response data for the 37 patients in Study 1200.32 with an uncommon mutation(s).

Please note that at the time of the primary snapshot, all but 5 of the 37 patients with uncommon mutations had completed their imaging so their tumor response data will not change. Of these 5 patients, 2 were continuing imaging at the time of the OS update.

Patients ongoing at primary snapshot but complete at OS update:

3214009 (Chemo): PD by independent review at primary analysis (13.8 months), PD at OS update by investigator (19.2 months).
3219004 (Chemo): SD by independent review/investigator at primary analysis, PD at OS update by investigator (24.8 months).
5302005 (Afatinib): PD by independent review at primary analysis (11.0 months), PD at OS update by investigator (20.8 months).

Patients ongoing at OS update:

3601024: (Afatinib): PR by independent review/investigator at primary analysis, still PR by investigator at OS update.
3603008: (Afatinib): PR by independent review/investigator at primary analysis, still PR by investigator at OS update.

In summary, new independent data will provide an update on tumor response for 3 patients (3219004, 3601024 and 3603008).

I hope this address you request ,but please let me know if you need further information/clarification.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Thursday, April 04, 2013 3:10 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

That is OK. Thank you again

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Thursday, April 04, 2013 3:05 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

We would like to have the trial statistician for Study 1200.32 confirm the results we will provide in response to the below request before sending to you. As he is located in the UK, we would like to wait until tomorrow morning before responding (due to the time difference). I regret the delay but hope this is okay.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Thursday, April 04, 2013 1:47 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Also please indicate

- if the response rates provided are confirmed(i.e. f/up scan after 30days) and
- Duration of response

Shakun

From: Malik, Shakun
Sent: Thursday, April 04, 2013 1:10 PM
To: 'ann.agnor@boehringer-ingelheim.com'
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Ann and Jim,

In RESPONSE TO REQUEST FOR INFORMATION – STUDY 1200.32 UPDATED Provided on January 28, table 4 2013 you provided a table (table 4) as investigator assessments of overall survival and other efficacy results for patients within the "Other" EGFR mutation because independent assessments have not been updated for the January 2013 database. Please provide us with updated data as per IRR.

Thank you
Shakun

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/s/

DEANNE R VARNEY
05/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 1, 2013

From: Deanne Varney DOP2/OHOP/CDER

Subject: NDA 201292 – Meeting with OC and DIDQ Regarding Manufacturing Site

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Attendees: Richard Pazdur, Tony Murgo, Shakun Malik, Deanne Varney, David Doleski, Mahesh Ramanadham, Carmelo Rosa, Alicia Mozzachio, Douglas Stern, Andrea Chamblee

Subject: Discuss the inspection of the BI DS/DP manufacturing site, the pending warning letter, and the impact of this letter on the upcoming action for afatinib.

Discussion during the meeting: The following points were noted during the meeting:

- DIDQ anticipates issuing the Warning Letter by COB on Friday, May 3, 2013, which will allow BI time to review the letter prior to the Late Cycle Meeting (LCM) on May 7, 2013
- DIDQ feels that BI should be able to respond adequately within 15-30 days
- DIDQ will expedite their review of BI's response once received, and noted that in this case if the response is adequate we can approve afatinib without a follow-up inspection
- During the LCM, DIDQ will reiterate to BI that per the warning letter, we expect a response within 15 days, and that if an adequate response is not received prior to the PDUFA date, the product cannot be approved
- DOP2 will provide DIDQ with a memo regarding the compelling medical need for afatinib

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/s/

DEANNE R VARNEY
05/01/2013

Varney, Deanne

From: Varney, Deanne
Sent: Tuesday, April 30, 2013 9:52 AM
To: Varney, Deanne
Subject: FW: NDA 201292 - afatinib request

From: Malik, Shakun
Sent: Monday, April 29, 2013 9:09 PM
To: ann.agnor@boehringer-ingelheim.com
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Ann,
In SAF-5, 59 cases were identified from the broad ILD SMQ, 28 cases were considered related to the study drug and 31 cases were considered not related to the study drug. In addition to the brief narration given in the ISS of these 31 patients, Are there additional narratives that have been submitted to the NDA?
Thank you
shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Thursday, April 18, 2013 6:39 AM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Here is the requested information on the 5 patients in Study 1200.32 who received 50 mg as a starting dose instead of 40 mg:

Pt 4101010: Had 28 days of afatinib 50 mg before being dose reduced to 40 mg due to a G2 rash.
Pt 4202004: Had 18 days of afatinib 50 mg before discontinuing due to G3 diarrhoea.
Pt 4310003: Is continuing on afatinib 50 mg after 3 years of exposure.
Pt 4807004: Had 12 days of afatinib 50 mg before being dose reduced due to G3 rash.
Pt 5604001: Had 64 days of afatinib 50 mg before being dose reduced due to G1 rash.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, April 17, 2013 5:04 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Thanks

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Wednesday, April 17, 2013 5:04 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Apologies that I read your message late today as I was out of the office. I will get an answer for you as soon as possible.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, April 17, 2013 4:22 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: NDA 201292 - afatinib request

Ann a quick question
Altogether 21 patients received 50 mg afatinib. Of those, 16 patients had been dose-escalated according to protocol; the remaining 5 patients erroneously received an afatinib starting dose of 50 mg instead of 40 mg.
Were these 5 patients deescalated to 40 mg dose?
How long were they on 50 mg dose?
Thanks
Shakun

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/s/

DEANNE R VARNEY
04/30/2013

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF INTERNAL MEETING MINUTES

Meeting Date and Time:	April 25, 2013
Meeting Location:	Teleconference
Application Number:	NDA 201292
Product Name:	Afatinib
Indication:	NSCLC
Applicant Name:	Boehringer Ingelheim
Type of Meeting:	Teleconference with Special Government Employee (SGE), Ms. Pamela Moffitt, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM)

FDA ATTENDEES
Anthony Murgo, Cross Discipline Team Leader
Gideon Blumenthal, Clinical Team Leader
Shakun Malik, Clinical Reviewer
Sean Khozin, Clinical Reviewer
Deanne Varney, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES
Ms. Pamela Moffitt

BACKGROUND: Ms. Pamela Moffitt agreed to serve and was cleared as an SGE for this NDA. Prior to this teleconference, background materials and draft product labeling were provided to Ms. Moffitt, along with two questions for Ms. Moffitt to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS: In this application, BI seeks the approval of Gilotrif (afatinib) for locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test.

FDA Questions for Discussion During Teleconference:

1. Does the risk/benefit ratio favor an indication of afatinib for first-line treatment of patients with metastatic non-small cell lung cancer with EGFR mutation(s)?

   Discussion: Ms. Moffitt noted that the afatinib arm demonstrated much higher toxicity than the chemotherapy arm, and there were more fatal outcomes in the afatinib arm than the chemotherapy arm. FDA noted that the chemotherapy was given for 6 cycles and then discontinued, whereas afatinib was given until disease progression, which can be for

a much longer period of time; however, FDA is aware that afatinib has potential toxicities. FDA inquired if, despite the noted toxicities, afatinib improved PFS enough to approve the indication?

Ms. Moffitt noted that it was her understanding that overall survival (OS) should be the primary endpoint. FDA noted that the OS benefit is reviewed to ensure it is not worse, but that it can be challenging to achieve an OS benefit with targeted therapies if patients cross-over after disease progression.

Ms. Moffitt noted that more Asians were enrolled in the study than non-Asians, and inquired if afatinib would benefit non-Asians proportionally. FDA stated that Asian vs. non-Asian was a stratification factor, and that the drug was equally effective in non-Asians and Asians.

Ms. Moffitt noted that a PFS benefit was demonstrated, and that as long as the patients can live with a good quality of life, then yes, the benefit outweighs the risk.

2. Should the label limit the indication of afatinib to patients with EGFR Exon 19 and Exon 21 mutations only?

Discussion: Ms. Moffitt initially noted that there is definite benefit in the exon 19 and 21 mutations, but would not limit the indication. FDA noted that, as demonstrated in Figure 5 of the background package, afatinib may be detrimental to patients with the "Other" mutations. Ms. Moffitt stated that she understands why FDA wants to limit the indication to the mutations that afatinib has been shown to have a clinical benefit for. FDA clarified that although the indication will be restricted to the exon 19 and 21 mutations, the uncommon mutations will not be contraindicated in the label. , If a physician feels a patient with an uncommon mutation might respond or that afatinib might be a good option, the physician could still treat these patients with afatinib. FDA further noted that the response rates for the uncommon mutations will be described in the product label.

Additional Discussion Points:

3. The PPI needs to be updated regarding when to take BRAND (1 hour before or 2 hours after a meal). FDA will ensure this is updated.

4. The PPI needs to be updated regarding when to take a missed dose of BRAND (b) (4) . FDA will ensure this is updated.

ATTACHMENTS: Background information provided to Ms. Moffitt via secure email communication on April 19, 2013.

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/s/

DEANNE R VARNEY
04/26/2013

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF INTERNAL MEETING MINUTES

Meeting Date and Time:	April 25, 2013
Meeting Location:	Teleconference
Application Number:	NDA 201292
Product Name:	Afatinib
Indication:	NSCLC
Applicant Name:	Boehringer Ingelheim
Type of Meeting:	Teleconference with Special Government Employee (SGE), Dr. Arun Rajan, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM)

FDA ATTENDEES
Anthony Murgo, Cross Discipline Team Leader
Gideon Blumenthal, Clinical Team Leader
Shakun Malik, Clinical Reviewer
Deanne Varney, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES
Dr. Arun Rajan

BACKGROUND: Dr. Arun Rajan agreed to serve and was cleared as an SGE for this NDA. Prior to this teleconference, background materials and draft product labeling were provided to Dr. Rajan, along with two questions for Dr. Rajan to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS: In this application, BI seeks the approval of Gilotrif (afatinib) for locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test.

FDA Questions for Discussion During Teleconference:

1. Does the risk/benefit ratio favor an indication of afatinib for first-line treatment of patients with metastatic non-small cell lung cancer with EGFR mutation(s)?

   Discussion: Dr. Rajan stated that a clinical benefit appears to have been demonstrated and that the benefit is consistent with what has been seen in previous studies. Therefore, the risk/benefit ratio is in favor of approving the indication for the first-line treatment of patients with metastatic non-small cell lung cancer with EGFR mutations.

2. Should the label limit the indication of afatinib to patients with EGFR Exon 19 and Exon 21 mutations only?

   Discussion: Dr. Rajan noted that the data demonstrated a much higher hazard ratio for the uncommon mutations, and that a clinical benefit was shown for the two common mutations but not for the uncommon mutations. Therefore, the benefit is more perceptible in the exon 19 and 21 mutations. Dr. Rajan also noted that clinical benefit in PFS is greater in the exon 19 mutation population than in the exon 21 (L858R) mutation population, but that both patient populations will probably benefit.

   Taking into account all of the data, Dr. Rajan believes the label should be restricted to the exon 19 and 21 mutations.

Additional Discussion Points:

3. Dr. Rajan inquired into the cause of the 8% discontinuation rate. FDA noted discontinuation in most patients was primarily due to disease progression and the 8% was due to drug related toxicities.

4. Dr. Rajan inquired if there is a recommendation in the label to monitor ejection fraction during treatment. FDA noted that there is not a blanket recommendation to monitor everyone at baseline, [redacted] (b) (4)

ATTACHMENTS: Background information provided to Dr. Rajan via secure email communication on April 19, 2013.

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/s/

DEANNE R VARNEY
04/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

DISCIPLINE REVIEW LETTER

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor
Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Please refer to your November 14, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afatinib tablets, 20 mg, 30 mg, 40 mg, (b) (4).

Our review of your submission is complete, and we have identified the following deficiencies:

Clinical and Statistical:

1. (b) (4)

Study 1200.23 (Lux Lung 1) was a Phase IIb/III randomized double-blind trial of afatinib plus best supportive care (BSC) versus placebo plus BSC in patients with non-small cell lung cancer after failure of erlotinib or gefitinib and who had previously received 1 or 2 lines of chemotherapy. The trial enrolled 585 patients who were randomized (2:1) to receive 50 mg afatinib orally once daily plus best supportive care (n=390) or placebo plus BSC (n=195).

The trial population was clinically enriched for EGFR mutations by requiring patients to have had prior EGFR-TKI therapy for at least 12 weeks. In the study 186/585 (32%) of the patients had tissue available for EGFR mutational status testing at either the local lab or central lab. There was a high degree of imbalance between the two arms on this retrospective analysis of EGFR mutation status with a high degree of discrepancy noted between the types of EGFR mutations reported by the central lab verses the local lab.

The study failed its primary endpoint of OS with the median OS for placebo of 12.0 months and afatinib of 10.8 months (HR=1.08; 95% confidence interval: 0.86 to 1.35).

[redacted] (b) (4) The study failed its primary endpoint of OS, had a marginal PFS benefit as secondary endpoint, and the population is poorly defined.

2. [redacted] (b) (4).

Of the patients treated with afatinib with a starting dose of 40 mg po per day:

- Only 16/230 patients were dose escalated to 50 mg
- Of these 16 patients, 13 received afatinib 50 mg for 21 days or more; 10 patients needed at least one dose reduction and, of these, 5 needed 2 dose reductions.

In addition, the supportive study 1200.22 (Lux Lung 2), an open-label, single-arm trial, using two starting doses of either 40 mg or 50 mg daily, showed a similar objective response rate for 40 and 50 mg doses and increased incidence and severity of adverse events with the 50 mg dose.

Clinical:

3. [redacted] (b) (4).

In pivotal study 1200.32 the majority of the patients enrolled had a tumor sample with an EGFR mutation categorized as either Exon 19 deletion [170/345 (49%)] or Exon 21 (L858R) [138/345 (40%)] while a small number [37/345 (11%)] were of the "Other" mutation category. Among this heterogeneous 'Other' category, consisting of a mix of 10 different genetic subtypes, 26 patients were assigned to afatinib and 11 to chemotherapy. On exploratory subgroup efficacy analysis of this subgroup of patients with 'Other' mutations, PFS and OS hazard ratios are in the direction favoring patients randomized to chemotherapy as compared to those randomized to afatinib.

Therefore, the indication for afatinib will be limited to patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Chemistry, Manufacturing, and Controls and Facilities:

4. BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG was inspected by the FDA from November 5, 2012 through November 12, 2012. This site is listed as the site of drug substance and drug product manufacturing. At the conclusion of this inspection, our field investigator conveyed deficiencies to the representative of the facility. The review of your responses, received between November 2012 and February 28, 2013, to the FDA form 483 issued at the close of this inspection is ongoing. At this time a final compliance status has not been determined. We remind you that, per 21 U.S.C. 505 (d)(3), grounds for denying approval of a pending application include finding 'the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength,

quality, purity.' We will communicate the final status of the review of your response when determined.

Pharmacology and Toxicology:

5. The pharmacology data submitted following several information requests to support the mechanism of action statement in the label was very limited in regard to the *in vitro* or *in vivo* effects of afatinib on inhibition of either common or rare EGFR mutations.

Clinical Pharmacology:

6. There are no currently identified clinical pharmacology deficiencies.

We are providing these comments to you to give you notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not necessarily reflect a final decision on the information reviewed and should not be construed to do so. These comments are subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Deanne Varney, Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Anthony J. Murgo, M.D.
Cross-Discipline Team Leader
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANTHONY J MURGO
04/25/2013

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF INTERNAL MEETING MINUTES

Meeting Date and Time:	April 24, 2013
Meeting Location:	Teleconference
Application Number:	NDA 201292
Product Name:	Afatinib
Indication:	NSCLC
Applicant Name:	Boehringer Ingelheim
Type of Meeting:	Teleconference with Special Government Employee (SGE), Dr. Steven Krasnow, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM)

FDA ATTENDEES
Anthony Murgo, Cross Discipline Team Leader
Gideon Blumenthal, Clinical Team Leader
Shakun Malik, Clinical Reviewer
Sean Khozin, Clinical Reviewer
James Xu, Clinical Reviewer
Deanne Varney, Regulatory Project Manager
Karen Boyd, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES
Dr. Steven Krasnow

BACKGROUND: Dr. Steven Krasnow agreed to serve and was cleared as an SGE for this NDA. Prior to this teleconference, background materials and draft product labeling were provided to Dr. Krasnow, along with two questions for Dr. Krasnow to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS: In this application, BI seeks the approval of Gilotrif (afatinib) for locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test.

FDA Questions for Discussion During Teleconference:

1. Does the risk/benefit ratio favor an indication of afatinib for first-line treatment of patients with metastatic non-small cell lung cancer with EGFR mutation(s)?

   Discussion: Dr. Krasnow believes the data supports the indication. FDA did not have any additional questions.

2. Should the label limit the indication of afatinib to patients with EGFR Exon 19 and Exon 21 mutations only?

   Discussion: Dr. Krasnow thinks the indication should be limited to the EGFR exon 19 and 21 mutations. He stated that it is valid to exclude the other mutations for which there are not enough data and restrict the indication to the exon 19 and 21 mutations.

   FDA inquired if the VA tests for mutations in adenocarcinoma. Dr. Krasnow stated that the VA tests for common mutations, but did not recall if they test for uncommon mutations, and did not recall the specific assay used.

Additional Discussion Points:

3. SGE Comments on Proposed Labeling:

   - Section 5.6: Advised that the section be reviewed for syntax
   - Section 7: Advised changing the wording (b) (4)
   - Section 2: Asked if it would be possible to state in the PI that afatinib can be dispersed in water and administered via a gastric tube, as the VA has many patients that have gastric tubes and are unable to take tablets. FDA noted that the applicant did not provide data to support this, but will send an information request to BI asking if they have any data to support dispersing in liquid.

ATTACHMENTS: Background information provided to Dr. Krasnow via secure email communication on April 19, 2013.

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/s/

DEANNE R VARNEY
04/25/2013

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, April 24, 2013 10:13 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Information Request

Hi Ann,

Please see the below information request for afatinib. Please provide a response at your earliest convenience.

If available, provide data to support the (b) (4) ***.***

Please confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
04/24/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 201292

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

ATTENTION: Ann Agnor, MS
Associate Director, Regulatory Affairs

Dear Ms. Agnor:

Please refer to your New Drug Application (NDA) dated November 14, 2012, received November 15, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Afatinib Tablets, 20 mg, 30 mg, 40 mg, (b) (4).

We also refer to your March 4, 2013, correspondence, received March 4, 2013, requesting review of your proposed proprietary name, Gilotrif. We have completed our review of the proposed proprietary name, Gilotrif and have concluded that it is acceptable.

The proposed proprietary name, Gilotrif, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 4, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Deanne Varney at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Kellie Taylor, PharmD, MPH
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
04/19/2013

Varney, Deanne

From: Varney, Deanne
Sent: Friday, April 19, 2013 1:52 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Proposed Labeling and PMC

Importance: High

Hello Ann,

Please find attached our proposed edits to the afatinib PI. In addition to these edits, please update all table and figure numbers as needed and correct formatting where required.

We also have the following comments on your carton and container labeling:

Container Labels and Carton Labeling:

1. The colors used to highlight and differentiate the 20 mg and 40 mg strength presentations are similar to the colors used for the three block color graphic on the principal display panel for all strengths. Because color is used to differentiate strength, using a similar color for the 20 mg and 40 mg strength that is also used to create a three block color graphic on the principal display panel may result in wrong product strength selection errors. Select a color for the 20 mg and 40 mg strength presentations that is not similar to the colors incorporated into the three block color graphic. Or, delete the three block color graphic or select different colors for the three block color graphic.

2. The color used for the strength presentation of the 40 mg afatinib product is very similar to the color used for the strength presentation of the currently marketed 5 mg Inlyta (Axitinib) product. Because the established names, axitinib and afatinib, are orthographically and phonetically similar and both products may be stored near each other on the pharmacy shelf, it is important to differentiate these products with different colors to mitigate the risk of wrong product selection. Select a color for the 40 mg afatinib strength presentation that is different than the color used for the strength presentation of the currently marketed 5 mg Inlyta (axitinib) product.

3. Delete or decrease the prominence of the graphic next to the proprietary and established names because it competes with other important information. If the graphic is decreased in prominence, then ensure there is sufficient white space between the proprietary and established names and the graphic.

4. Revise the statement [redacted] (b) (4) to read "Attention: Dispense and Store Medication in the Original Container to Protect from Light and Humidity". The revised statement will provide information for the pharmacist and patient. If space constraints do not permit the entire statement, then consider deleting the rationale, "to Protect from Light and Humidity".

5. Ensure the established name is at least ½ the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printer features per 21 CFR 201.10(g)(2). Consider revising the established name to appear in a black color with a bolded font.

6. Un-bold the statement "30 tablets" wherever it occurs.

Container Label:

1. The Quick Response (QR) code is too prominent and competes with the strength statement and other important information. Decrease the size of the QR code.

Carton Labeling:

1. Move the statement "30 tablets" on the top and side panels away from the strength presentation. Post marketing data shows that confusion with the strength and bottle count can occur when they are in close proximity with each other.

Please review our proposed edits and comments to the afatinib labeling and determine if you are in agreement with the proposed edits. If so, please accept all edits and submit the clean labeling to your NDA by Friday, April 26th. If you have additional edits to propose, please accept the edits you agree with, make any additional edits in track changes, and submit the counterproposal to your NDA by **Friday, April 26th,** with a courtesy copy to me via email.

I have also attached a post-marketing commitment. Please review this PMC and the proposed milestone date. If you are in agreement, please submit this proposed PMC and milestone date as a formal amendment to your NDA.

Please confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DEANNE R VARNEY
04/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 19, 2013

From: Deanne Varney DOP2/OHOP/CDER

Subject: NDA 201292 – Meeting with OC and DIDQ Regarding Manufacturing Site

---

Attendees: Richard Pazdur, Patricia Keegan, Tony Murgo, Gideon Blumenthal, Shakun Malik, Deanne Varney, Ilisa Bernstein, Michael Smedley, David Doleski, Mahesh Ramanadham, Carmelo Rosa, Alicia Mozzachio, Mary Farbman, Douglas Stern, Andrea Chamblee

Subject: Discuss the inspection of the BI DS/DP manufacturing site, the pending warning letter, and the impact of this letter on the upcoming action for afatinib.

Discussion during the meeting: The following points were noted during the meeting:

- DIDQ will discuss options internally for possible ways to "carve out" afatinib to allow for approval or for distribution without approval
- DOP2 would prefer any option that allows for approval of afatinib
- There is a Late Cycle Meeting with BI on May 7th – the facilities group will attend in order to discuss the outstanding manufacturing issues
- DIDQ hopes to issue the warning letter prior the May 7th meeting with BI
- The PDUFA date for afatinib is July 15th – DIDQ noted that this might allow time for BI to respond to the warning letter and be re-inspected, potentially opening up more channels for carving out afatinib for approval
- Another internal meeting will be held prior to the May 7th meeting with BI to discuss options

---

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/s/

DEANNE R VARNEY
04/19/2013

Varney, Deanne

From: Malik, Shakun
Sent: Wednesday, April 17, 2013 4:22 PM
To: ann.agnor@boehringer-ingelheim.com
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: NDA 201292 - afatinib request

Ann a quick question
Altogether 21 patients received 50 mg afatinib. Of those, 16 patients had been dose-escalated according to protocol; the remaining 5 patients erroneously received an afatinib starting dose of 50 mg instead of 40 mg. Were these 5 patients deescalated to 40 mg dose?
How long were they on 50 mg dose?
Thanks
Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Friday, April 05, 2013 2:40 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

We can confirm what you stated below is correct, as shown in Listing 96.1: The mutation sub-types of the 4/23 afatinib-treated patients achieving PR is correct (L858R+T790M; G719X; L858R+S768I; and S768I). None achieved a CR, with 3 being not evaluable.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Friday, April 05, 2013 1:50 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Thanks.
Please confirm the following
of 23 evaluable patients in Afatinib arm, none achieved a complete response, and four achieved a confirmed partial response 1 in each.
L858R and T790M, G719X, L858R+S768I and S768I

Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Friday, April 05, 2013 7:41 AM

To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

Please find attached Table 96.1 "Confirmed and unconfirmed responses with durations (Investigator assessment) for patients with uncommon mutations". This table includes the unconfirmed and confirmed response data for the 37 patients in Study 1200.32 with an uncommon mutation(s).

Please note that at the time of the primary snapshot, all but 5 of the 37 patients with uncommon mutations had completed their imaging so their tumor response data will not change. Of these 5 patients, 2 were continuing imaging at the time of the OS update.

Patients ongoing at primary snapshot but complete at OS update:

3214009 (Chemo): PD by independent review at primary analysis (13.8 months), PD at OS update by investigator (19.2 months).
3219004 (Chemo): SD by independent review/investigator at primary analysis, PD at OS update by investigator (24.8 months).
5302005 (Afatinib): PD by independent review at primary analysis (11.0 months), PD at OS update by investigator (20.8 months).

Patients ongoing at OS update:

3601024: (Afatinib): PR by independent review/investigator at primary analysis, still PR by investigator at OS update.
3603008: (Afatinib): PR by independent review/investigator at primary analysis, still PR by investigator at OS update.

In summary, new independent data will provide an update on tumor response for 3 patients (3219004, 3601024 and 3603008).

I hope this address you request ,but please let me know if you need further information/clarification.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: (b) (6)
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Thursday, April 04, 2013 3:10 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

That is OK. Thank you again

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Thursday, April 04, 2013 3:05 PM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Dr. Malik,

We would like to have the trial statistician for Study 1200.32 confirm the results we will provide in response to the below request before sending to you. As he is located in the UK, we would like to wait until tomorrow morning before responding (due to the time difference). I regret the delay but hope this is okay.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Thursday, April 04, 2013 1:47 PM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Also please indicate

- if the response rates provided are confirmed(i.e. f/up scan after 30days) and
- Duration of response

Shakun

From: Malik, Shakun
Sent: Thursday, April 04, 2013 1:10 PM
To: 'ann.agnor@boehringer-ingelheim.com'
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Ann and Jim,

In RESPONSE TO REQUEST FOR INFORMATION – STUDY 1200.32 UPDATED Provided on January 28, table 4 2013 you provided a table (table 4) as investigator assessments of overall survival and other efficacy results for patients within the "Other" EGFR mutation because independent assessments have not been updated for the January 2013 database. Please provide us with updated data as per IRR.

Thank you
Shakun

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/s/

DEANNE R VARNEY
04/18/2013

Varney, Deanne

From: Varney, Deanne
Sent: Friday, April 12, 2013 12:00 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Information Request

Hi Ann,

Please see the below information request, and provide a reply via email by **12PM on Monday, April 15th.**

Additional figures are needed for the package insert. For Study 32, submit forest plots showing the HR for PFS and OS (January update) for the following EGFR subgroups: Common (Del 19, L858R), Del19, L858R, Other. See attached example, but please ensure that the x-axes are clearly marked, and leave off the N for each group, as these will be provided in a table.

Please confirm receipt.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
04/12/2013

TEAM MEETING MINUTES
April 8, 2013

New NDA 201292
Afatinib
Boehringer Ingelheim

Submission Date: November 14, 2012
Received Date: November 15, 2012
PDUFA Date: July 15, 2013
Corresponding PMA Goal Date: June 5, 2013

Proposed Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test

Current Review Team for NDA 201292:
Patricia Keegan, Director DOP2
Deanne Varney, Regulatory Health Project Manager
Karen Jones (CPMS)
Shakun Malik, Medical Officer
Anthony Murgo, Medical Officer (CDTL)
Jonathan Norton, Statistics
Kun He, Statistics (TL)
Runyan Jin, Clinical Pharmacology
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology (TL)
Dubravka Kufrin, Non-Clinical
Whitney Helms, Non-Clinical (TL)
Li Shan Hsieh, Quality
Liang Zhou, Quality (TL)
Ali Al Hakim, Quality (TL)
Jewell Martin, Quality (ONDQA RPM)
Angelica Dorantes, Biopharmaceutics TL
Elsbeth Chikhale, Biopharmaceutics Reviewer
Rosane Charlab Orbach, Genomics Reviewer

Consults for NDA 201292:
James Schlick, OSE Proprietary Name Reviewer and DMEPA Reviewer
Todd Bridges, DMEPA TL
Bob Pratt, DRISK
Cynthia Lacivita, DRISK TL
Kate Coyle, DPV

Corrinne Kulick, DPV TL
Quynh-Van Tran, OPDP Professional Reviewer
Shenee Toombs, OPDP, Consumer Reviewer
Lauren Iacono-Connors, OSI
Tammy Brent-Howard, Maternal Health
Carrie Ceresa, Maternal Health TL
Karen Dowdy, PLT
Barbera Fuller, PLT (TL)
Adel Abou-Ali, DEPI

CDRH Review Team for PMA:
Jennifer Shen
Maria Chan

Review Status:

- Priority Review requested (PDUFA V --- 8 month review)
- Categorical Exclusion from environmental assessment requested
- Orphan designation granted; exempt from PREA
- Requested waiver of half-page Highlights
- The clinical development of afatinib has been conducted under INDs 67969 and 114002.

Agenda Items:

1. Discuss Target Action Date and CDRH Review Status

Discussion: CDRH Update: Official submission from Qiagen to CDRH expected June 11, 2013. CDRH is unlikely to be ready to take an action on the PMA before July. CDRH will have 90 days from the date of the new submission to review the information. If the NDA is CR'd, the PMA will be CR'd as well.

2. Reminder: Upcoming Late Cycle Meeting

Discussion: The purpose of the late cycle meeting scheduled with BI on May 7th will be to discuss the status of the review of the application. Potential topics for discussion include:

- Major deficiencies identified to date
- Current assessment of need for REMS or other risk management actions
- Information Requests
- Additional data or analyses the applicant may wish to submit (the review team and applicant will discuss whether such data would be reviewed in the current review cycle, and if so, whether the submission would be considered a major amendment)

The internal meeting is scheduled for 4/17, and the briefing package is due to BI on 4/25.

3. Reminder: Must send proposed labeling and PMR/PMCs to BI by April 19, 2013

Discussion: One clinical pharmacology PMR for hepatic impairment, one clinical PMC for the final OS analysis. (b) (4) [redacted] CMC will confirm if there are any proposed PMRs or PMCs.

4. Reminder: Discipline Review Letters

Discussion: Clinical, statistics, genomics, nonclinical, and clinical pharmacology will issue one DR letter. The team will look into who the signatory should be on the combined DR letter. ONDQA will determine if they will issue a separate letter or in the combined letter.

5. Should specific companion diagnostic be named in the PI, and if so, where?

Discussion: This issue is being discussed off-line.

6. Milestone Goals Remaining:

Milestone	8 month review July 15, 2013	6.5 month review June 5, 2013
Acknowledgment Letter	November 29, 2012 ***Issued November 20, 2012***	November 29, 2012 ***Issued November 20, 2012***
Priority Review Determination/Filing Issues Identified Letter	January 14, 2013 ***Issued January 11, 2013***	January 14, 2013 ***Issued January 11, 2013***
Mid-Cycle Communication	February 28, 2013 ***Scheduled February 20, 2013***	February 28, 2013 ***Scheduled February 20, 2013***
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	April 19, 2013	April 19, 2013
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	April 26, 2013	April 26, 2013
Issue Discipline Review Letters	April 26, 2013	April 26, 2013
Late Cycle Meeting	May 7, 2013 *(Briefing package due*	May 7, 2013 *(Briefing package due*

	4/25/13)	*4/25/13)*
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 April 22, 2013 April 25, 2013 June 20, 2013 July 5, 2013 July 15, 2013	 April 22, 2013 April 25, 2013 May 11, 2013 May 26, 2013 June 5, 2013
Compile and circulate Action Letter and Action Package	June 25, 2013	May 16, 2013
FINAL Action Letter Due	**July 15, 2013**	**June 5, 2013**

7. Review Issues/Updates:

a. Clinical: None

b. Statistical: None

c. Genomics: None

d. Nonclinical: None

e. Clinical Pharmacology: None

f. CMC/Biopharm: None

g. CDRH: None

8. Inspections:

a. Clinical site inspections update: All inspections complete. Only one site had a minor 483 (Germany). All other sites were NAI.

b. Manufacturing site inspections update:

Most recent compliance status:

- Boehringer Ingelheim Pharma GmbH & Co. KG: Warning letter will be issued and firm is under import alert. Unlikely that this site will be acceptable before the PDUFA date. The team will discuss if the 483 form should be included in the LCM background package.
- (b) (4): Acceptable

- [redacted]: Acceptable

9. Upcoming Internal Team Meetings:

i. **Labeling Meetings (suggested section groupings):**

April 10, 2012: If needed

May 8, 2013: Discuss OPDP and/or applicant comments, if needed

ii. **Remaining Monthly Team Meetings:**

May 20, 2013

June 5, 2013

July 3, 1013

iii. **Wrap- Up Meeting**: May 6, 2013

iv. **Late Cycle Meeting with Applicant:** May 7, 2013

8. ODAC Not Needed

9. Consults/Collaborative Reviewers:

OPDP	Quynh-Van Tran - professional reviewer Shenee Toombs - consumer reviewer Olga Salis – RPM
OSE	Sue Kang - OSE RPM Sean Bradley - OSE RPM TL *DMEPA to review carton/container and proprietary name review (request received 11/27/12) – James Schlick Todd Bridges – DMEPA TL DEPI: Adel Abou-Ali DRISK: Bob Pratt/Cynthia LaCivita DPV: Kate Coyle/ Corrinne Kulick

Maternal Health	Tammie Brent-Howard - Reviewer Carrie Ceresa – TL Melissa Tassinari
Facility/OMPQ	The sites have been entered in EES.
OSI	Lauren Iacono-Connors assigned, site selection in progress
Pediatric Page/PeRC	Full Waiver Requested ***PeRC scheduled March 27, 2013***
Patient Labeling Team	Karen Dowdy – Reviewer Barbara Fuller - TL
SEALD	*Consult sent 11/21/12*
QT-IRT	*Consult sent 12/3/12*
SGE's or Patient Representatives	Dr. Malik to work with (b) (4)

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/s/

DEANNE R VARNEY
04/08/2013

From: Martin, Jewell
To: "james.segretario@boehringer-ingelheim.com"
Subject: NDA 201292 CMC Information Request
Date: Monday, April 08, 2013 12:49:00 PM

Hello Mr. Segretario,

Below you will find a CMC Information Request for NDA 201292. Please respond by COB April 11, 2013.

1. Revise the dissolution acceptance criterion [redacted] (b) (4) to Q [redacted] (b) (4) at 15 minutes. Submit a revised drug product specification table.

2. Provide an explanation for the observed difference at the early time points between the dissolution profiles of the 20 mg and 30 mg drug product batches manufactured in Biberbach and Ingleheim. (Figures 30 and 31, section 3.2.P.2 Pharmaceutical Development). Indicate if there are any differences between the two manufacturing sites that could have caused the observed difference in the initial phase of the dissolution profiles of the drug products made at each site.

Please confirm receipt of this email.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP
Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2072
jewell.martin@fda.hhs.gov

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/s/

JEWELL D MARTIN
04/08/2013

Varney, Deanne

From: Malik, Shakun
Sent: Thursday, April 04, 2013 1:47 PM
To: ann.agnor@boehringer-ingelheim.com
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Also please indicate

- if the response rates provided are confirmed(i.e. f/up scan after 30days) and
- Duration of response

Shakun

From: Malik, Shakun
Sent: Thursday, April 04, 2013 1:10 PM
To: 'ann.agnor@boehringer-ingelheim.com'
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com; Charlab Orbach, Rosane
Subject: RE: NDA 201292 - afatinib request

Dear Ann and Jim,

In RESPONSE TO REQUEST FOR INFORMATION – STUDY 1200.32 UPDATED Provided on January 28, table 4 2013 you provided a table (table 4) as investigator assessments of overall survival and other efficacy results for patients within the "Other" EGFR mutation because independent assessments have not been updated for the January 2013 database. Please provide us with updated data as per IRR.

Thank you
Shakun

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/s/

DEANNE R VARNEY
04/04/2013

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, April 03, 2013 10:13 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 Nonclinical Information Request

Hi Ann,

Please see the below information request from the nonclinical review team. Please provide a response at your earliest convenience. If it is possible to respond by 2PM today, that would be helpful. If not, at your earliest convenience will be fine.

If available, please provide a table explaining the EGFR mutation status of cell lines used in the pharmacology studies included in the NDA or direct us to where this information can be found in the application.

Please confirm receipt.

Thank you!
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
04/03/2013

Varney, Deanne

From: Malik, Shakun
Sent: Tuesday, April 02, 2013 1:37 PM
To: ann.agnor@boehringer-ingelheim.com
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: afatinib request 12Mar2013

Dear Ann,

Please provide the following information for Geriatric population:

1) The number enrolled in (n= %_) ≥ 65 yrs.' and ≥75yrs in both SAF 5 and SAF 1
2) Please provide efficacy for PFS and OS in SAF1.
3) Please provide toxicity differences >10% in SAF5.

Thanks
Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Tuesday, April 02, 2013 11:24 AM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: afatinib request 12Mar2013

Dear Shakun,

Thank you kindly, this is very clear now. We appreciate the "heads-up" on these labeling proposals.

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Tuesday, April 02, 2013 11:02 AM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: afatinib request 12Mar2013

Thanks Ann.
Please see the response below.
Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Tuesday, April 02, 2013 10:52 AM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: afatinib request 12Mar2013

Dear Dr. Malik,

We confirm that the percentages in the proposed Table 3 are based on CTCAE grading. We agree to use 5% as the cut-off.

We do still have a question for clarification…

As we understand it, you are proposing to have Table 3 "**Adverse Reactions of Laboratory Abnormalities from the Investigations SOC Reported in ≥5% of BRAND-Treated Patients in LUX-Lung 3"** as a separate table from the existing Table 2 ("Adverse Reactions Reported in ≥10% of BRAND-Treated Patients in LUX-Lung 3"). (b) (4)

(b) (4)

Yes, we will separate all relevant labs from table 2 and put table 3 as separate(labs only).
To keep the label consistent with others we will be combining Grade 3 and 4 abnormalities.

Table 3 Adverse Reactions of Laboratory Abnormalities from the Investigations SOC Reported in ≥5% of BRAND-Treated Patients in LUX-Lung 3

	BRAND n=229		Pemetrexed/Cisplatin n=111	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	%	%	%	%
Alanine aminotransferase increased	(b) (4)			
Hypokalaemia[1]				
Aspartate aminotransferase increased				

(b) (4)

Kind regards,
Ann

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Tuesday, April 02, 2013 9:49 AM
To: Agnor,Ann (DRA) BIP-US-R
Cc: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne; Love,James (BDM) BIP-US-R
Subject: RE: afatinib request 12Mar2013

We have internally decided to have laboratory abnormalities as noted in clinical trial 1200.32 scheduled or unscheduled as table 3.

After I sent you e-mail last night I thought about it and think that if we have lab abnormalities in the table, we do not need the text.

In that case please confirm that the table 3 is accurate and this is based on CTAE grading as is table 2.
I prefer to include >5% since you had it in the text. [redacted (b) (4)].
Let me know what you think.

Thanks
I will be glad to discuss this with you if needed.

Shakun

From: ann.agnor@boehringer-ingelheim.com [mailto:ann.agnor@boehringer-ingelheim.com]
Sent: Tuesday, April 02, 2013 8:41 AM
To: Malik, Shakun
Cc: dennis.obrien@boehringer-ingelheim.com; Varney, Deanne; james.love@boehringer-ingelheim.com
Subject: RE: afatinib request 12Mar2013

Dear Dr. Malik,

Dennis and I spoke this morning and this response reflects our discussion. Our intention was to provide the frequencies of AEs (≥ 10%) in the AE table (Table 2) and liver laboratory abnormalities separately in text. Is it your intention to include a separate AE table of investigations abnormalities and not to include a table of actual laboratory abnormalities?

It may be helpful for us to know how you envision these tables/text the final labeling so we can accommodate your request. Perhaps a brief phone call would help to clarify for us so we can determine if we can meet the noon deadline. Please let us know if you have time this morning.

Kind regards,
Ann

Boehringer Ingelheim

Ann Agnor
Associate Director, Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, Connecticut
P: 203 798 5346 :: [redacted (b) (6)]
ann.agnor@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Monday, April 01, 2013 8:47 PM
To: O'Brien,Dr.,Dennis (DSI) BIP-US-R; Love,James (BDM) BIP-US-R
Cc: Varney, Deanne; Agnor,Ann (DRA) BIP-US-R
Subject: RE: afatinib request 12Mar2013

Thank you for the explanation. Can you please provide me only with CTCAE grades that matches the text and the table for study 1200.32, otherwise it will be hard for the physicians to follow. Please provide by noon tomorrow.
Thanks
Shakun

From: dennis.obrien@boehringer-ingelheim.com [mailto:dennis.obrien@boehringer-ingelheim.com]
Sent: Monday, April 01, 2013 5:23 PM
To: Malik, Shakun; james.love@boehringer-ingelheim.com
Cc: Varney, Deanne; ann.agnor@boehringer-ingelheim.com
Subject: RE: afatinib request 12Mar2013

Dear Dr. Malik
As the Team Member Drug Safety, please allow me to address this response as Jim is travelling.
The differences in values depend on whether you are considering adverse event data or laboratory data.

Adverse events
The frequency of 17.5% represents pooled hepatic AE data of all hepatic AEs from the hepatic SMQs used. It includes AEs of hepatic enzyme elevations as well as any other hepatic AEs. (See ISS table 2.8.8.1.1 or SCS table 2.1.12.5: 1 Incidence of hepatic adverse events using SMQs). Table 3 included in the email below is the AE frequency of individual hepatic AEs in study 1200.32 (e.g. ALT increased).

Table 3 Frequency of patients with adverse events form the MedDRA investigations SOC1 for Study 1

	BRAND n=229		**Pemetrexed/Cisplatin n=111**	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Preferred term	%	%	%	%
Alanine aminotransferase increased	(b) (4)			
Hypokalaemia[1]				
Aspartate aminotransferase increased				(b) (4)

ALT laboratory elevations

For the statement:

(b) (4)

The source of this data is the actual hepatic enzyme elevations laboratory data from study 1200.32. (See ISS table 2.8.8.2.2 or SCS table 2.1.12.5: 2 Incidence of Liver enzyme elevations..). Please note the ISS/SCS table include the classic ALT categories of ALT 3-5x, 5-10x, 10-20x. However, since CTCAE grade 2 is defined as 2.5-5xULN, an additional analysis provides the frequency of ALT enzymes for CTCAE grade 2 (2.5-5xULN), as provided below:

BI Trial No.: x12005f1 Table 2.8.8.2.2 Frequency of patients with liver enzyme elevations, by treatment (SAF-1 and SAF-2)

	SAF-1 Control N (%)	SAF-1 40 mg N (%)2	Hazard ratio (95% C.I.) significance level	SAF- N (%
Total treated	111 (100.0)	229 (100.0)		497
Mean and (SD) time at risk (days)	113 (43)	355 (203)		326
Maximum ALT				
>2.5x ULN and <=5x ULN	4 (3.6)	18 (7.9)		36
>5x ULN and <=10x ULN	1 (0.9)	6 (2.6)		11
>10x ULN and <=20x ULN	1 (0.9)	2 (0.9)		3
>20x ULN	0 (0.0)	0 (0.0)		0
Maximum ALT >5x ULN	2 (1.8)	8 (3.5)		14
95% confidence interval	(0.22, 6.36)	(1.52, 6.77)		(1
			1.11 (0.23, 5.43) p=0.9004	
Incidence density (event / patient years)	0.059	0.037		0.

Therefore the laboratory ALT elevations of CTCAE grade 2 are 3.6% and 7.9% and grade 3 (5-20x) are 1.8 and 3.5% for chemotherapy and afatinib respectively.

Sincerely,
Dennis

Boehringer Ingelheim

Dennis O'Brien, MD
Medical Director, Global Safety Evaluations, Oncology
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT
P: 203 791 6466:: (b) (6)
dennis.obrien@boehringer-ingelheim.com

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Monday, April 01, 2013 3:35 PM
To: Love,James (BDM) BIP-US-R
Cc: Varney, Deanne; Agnor,Ann (DRA) BIP-US-R; O'Brien,Dr.,Dennis (DSI) BIP-US-R
Subject: RE: afatinib request 12Mar2013

Dear Jim,

I have a question

Following is the label from BI and the table you sent me re lab results. The numbers are different. Please explain.
thanks
shakun

(b) (4)

Table 3 Frequency of patients with adverse events form the MedDRA investigations SOC1 for Study 1

	BRAND n=229		Pemetrexed/Cisplatin n=111	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Preferred term	%	%	%	%
Alanine aminotransferase increased	(b) (4)			
Hypokalaemia[1]				
Aspartate aminotransferase increased				
(b) (4)				

From: james.love@boehringer-ingelheim.com [mailto:james.love@boehringer-ingelheim.com]
Sent: Wednesday, March 13, 2013 2:15 PM
To: Malik, Shakun
Cc: Varney, Deanne; ann.agnor@boehringer-ingelheim.com; dennis.obrien@boehringer-ingelheim.com
Subject: RE: afatinib request 12Mar2013

Dear Dr. Malik:

Dr. O'Brien and I have revised the tables as you requested.

In this "Investigations" table I have removed (b) (4) because it appears in Table (b) (4). In addition, I have replaced (b) (4) in the Investigations table with the grouped PT of "hypokalemia". The grouped PT of hypokalemia includes blood potassium decreased from the Investigations SOC and hypokalemia from the Metabolism and nutrition disorders SOC.

It is my understanding that this addresses all of the current requests. Please let me know if anything else is needed.

Sincerely,
Jim

Boehringer Ingelheim

James T. Love, M. Stat., PSTAT®
Senior Principal Biostatistician, Oncology
Biometrics and Data Management Department
Boehringer Ingelheim Pharmaceuticals, Inc.
PO Box 368
Ridgefield, Connecticut 06877
Office: 203 798-4253
Mobile: (b) (6)
Fax: 203 837-4253

Sincerely,
Jim

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Wednesday, March 13, 2013 11:09 AM
To: Love,James (BDM) BIP-US-R
Subject: FW: afatinib request 12Mar2013

Jim,

1. In table 2 compared to Investigations table you sent

   Weight decreased [redacted] (b) (4) is different (reverse)

   Please confirm the correct numbers.

2. Please take out [redacted] (b) (4) and put in the investigational table.
3. Please make investigational table similar to the table (b) with Brand in first and include only the (b) (4) toxicity from the brand.

From: james.love@boehringer-ingelheim.com [mailto:james.love@boehringer-ingelheim.com]
Sent: Tuesday, March 12, 2013 2:04 PM
To: Malik, Shakun
Cc: ann.agnor@boehringer-ingelheim.com; dennis.obrien@boehringer-ingelheim.com; Varney, Deanne
Subject: afatinib request 12Mar2013

Dear Dr. Malik:

Please review our interpretations of your requests and the attached responses that Dr. O'Brien and I have prepared.

1. FDA request:

   Grade 3 cutaneous toxicity characterized by bullous, blistering, and exfoliating lesions occurred in two patients in SAF 5. Please confirm if any such case were reported in 1200.32?

   BI response:

   For SAF -5, the SMQ of Severe cutaneous adverse reactions indentified 6 patients with grade 3 AEs.

   There was one patient from 1200.32 with an AE of grade 3 exfoliative rash. For this non serious AE, the patient continued on therapy after dose reduction and recovered.
   There were no events of Stevens Johnson syndrome in 1200.32.

2. FDA request:

   Provide a table of adverse events based upon labs for trial 1200.32.

   "We do not need to identify which was scheduled and or unscheduled but all the labs available to you associated with AE or not as labs may be abnormal without being reported as AE by the investigator."

BI response:

The attached document contains a table of all AEs for preferred terms form the MedDRA "Investigations " SOC.

However, we interpret your later email message (see quoted text above) as a request for a table of Grade 3 and 4 lab tests. We are in the process of producing a table for trial 1200.32 that will display two columns: (i) all Grades≥1 and (ii) Grade 3 and 4, for the following lab tests:

- *Low values (–): HGB, WBC, PLTCT, K, NA*
- *High values (+): SGOT, SGPT, CRE, TBILI*

Please confirm whether this table of abnormal labs will suffice.

3. FDA request:

   Revise table of adverse reactions for the proposed label.

   BI response:

   We have combined Grade 3 and 4 AEs in the attached document. The document is provided in word format so that you can make changes as needed. We are in the process of calculating the percentages for Rash and Dermatitis acneiform combined and will send an update once this has been completed.

Sincerely,
Jim

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Tuesday, March 12, 2013 7:41 AM
To: Love,James (BDM) BIP-US-R
Cc: Agnor,Ann (DRA) BIP-US-R; O'Brien,Dr.,Dennis (DSI) BIP-US-R; Varney, Deanne
Subject: RE: IR re toxicities Afatinib

Dear Jim,
Good morning,

Request following for the revised table 2 in the label.

1. Take out [redacted] (b) (4) from this table to be incorporated to the lab table.
2. Combine grade 3 and 4 together
3. Rash and acneform rash numbers should be together

Thanks

Shakun

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Sent: Monday, March 11, 2013 5:55 PM
To: Malik, Shakun
Cc: ann.agnor@boehringer-ingelheim.com; dennis.obrien@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: IR re toxicities Afatinib

Dear Dr. Malik:

We are in the process of preparing these requests and will respond more fully tomorrow.

For the request for lab AE (#2 below), we propose to provide a table of all AE , by preferred terms from the MedDRA "Investigations" SOC.
We cannot directly identify those AE associated with a lab from a scheduled visit from those associated with an unscheduled visit.

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Here are additional inquiries and requests

4. Grade 3 cutaneous toxicity characterized by bullous, blistering, and exfoliating lesions occurred in two patients in SAF
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if any such case were reported in 1200.32?

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3 and 4 (please combine 3 and 4)

6. Please combine Grade 3 & 4 toxicities together in Table 2 of the label in one column.

You may send the table for me edit and put in the label

Thanks

Shakun

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEANNE R VARNEY
04/02/2013

Varney, Deanne

From: Malik, Shakun
Sent: Monday, April 01, 2013 3:35 PM
To: james.love@boehringer-ingelheim.com
Cc: Varney, Deanne; ann.agnor@boehringer-ingelheim.com; dennis.obrien@boehringer-ingelheim.com
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(b) (4)

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James T. Love, M. Stat., PSTAT®
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PO Box 368
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Shakun

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/s/

DEANNE R VARNEY
04/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 25, 2013

From: Deanne Varney, RPM, DOP2/OHOP/CDER/FDA

Subject: NDA 201292

TELECONFERNCE

Sponsor Attendees:

Clinical:

Mehdi Shahidi, MD	Leader Clinical Development Afatinib
Dennis O'Brien, MD	Team Member, Drug Safety
Sven Wind, PhD	Project Pharmacokineticist
Ellen Gold, MD	Global Safety Evaluation, Oncology
Victoria Zazulina, MD	Leader Clinical Development Afatinib NSCLC
Vikram Chand, MD	Team Member Medicine, Oncology

Nonclinical/CMC:

James Segretario, PhD	Director, CMC Regulatory Affairs

Biometrics & Data Management:

James Love, M. Stat.	Project Statistician
Julie Cong, PhD	Project Statistician

Regulatory:

Ann Agnor, MS	Regulatory Affairs US
Pamela Strode	Executive Director, Regulatory Affairs
David Jones, MD	Regulatory Area Lead, Oncology
Thorsten Laux , PhD	Global Regulatory Affairs Manager

FDA Attendees:

Deanne Varney	Regulatory Project Manager, DOP2
Patricia Keegan	Director, DOP2
Anthony Murgo	Cross Discipline Team Leader, DOP2

Objectives:

Confirm that Boehringer Ingelheim (BI) understands (b) (4)

(b) (4)

Discussion:

(b) (4)

BI stated that they understand (b) (4) however, they will be submitting an additional study to IND 114002 (b) (4) This submission is 1500 pages, and includes demographics, safety, and efficacy analyses. BI inquired into whether or not this should also be submitted to NDA 201292. FDA stated that this study should not be submitted to the NDA at this time. FDA will review the submission under the IND, and will follow-up with BI if there are any questions.

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/s/

DEANNE R VARNEY
03/25/2013

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, March 21, 2013 11:25 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: NDA 201292 Information Request - Investigator Brochure

Hi Ann,

It appears that the only Investigator Brochure provided by BI in NDA 201292 was for BIBF-1120 (in response to a clinical pharmacology information request), and that an IB for BIBW-2992 has not been provided. Can you please submit the IB for BIBW-2992 to your NDA 201292? And also provide a copy of the current IB to me via email by COB today?

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
03/21/2013

Varney, Deanne

From: Malik, Shakun
Sent: Wednesday, March 13, 2013 10:00 AM
To: james.love@boehringer-ingelheim.com
Cc: Norton, Jonathan; Varney, Deanne
Subject: IR

Dear Jim,
Thank you for your help.

Please revise your table 5 in the label to include confirmed response rates and duration of response and send it by noon today

Shakun

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/s/

DEANNE R VARNEY
03/13/2013

Varney, Deanne

From: Malik, Shakun
Sent: Monday, March 11, 2013 4:07 PM
To: james.love@boehringer-ingelheim.com
Cc: ann.agnor@boehringer-ingelheim.com; dennis.obrien@boehringer-ingelheim.com; Varney, Deanne
Subject: RE: IR re toxicities Afatinib

Jim,

Here are additional inquiries and requests

1) Grade 3 cutaneous toxicity characterized by bullous, blistering, and exfoliating lesions occurred in two patients in SAF 5. Please confirm
if any such case were reported in 1200.32?

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3 and 4 (please combine 3 and 4)

3) Please combine Grade 3 & 4 toxicities together in Table 2 of the label in one column.
You may send the table for me edit and put in the label

Thanks

Shakun

From: james.love@boehringer-ingelheim.com [mailto:james.love@boehringer-ingelheim.com]
Sent: Monday, March 11, 2013 11:48 AM
To: Malik, Shakun
Cc: ann.agnor@boehringer-ingelheim.com; dennis.obrien@boehringer-ingelheim.com; Varney, Deanne
Subject: FW: IR re toxicities Afatinib

Dear Dr. Malik:

Dr. O'Brien and I have reviewed the questions and have responded below.

Please let us know if any further clarification is needed.

Sincerely,
Jim

From: Malik, Shakun [mailto:Shakuntala.Malik@fda.hhs.gov]
Sent: Monday, March 11, 2013 5:26 AM
To: Love,James (BDM) BIP-US-R

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/s/

DEANNE R VARNEY
03/11/2013

Varney, Deanne

From: Malik, Shakun
Sent: Monday, March 11, 2013 5:26 AM
To: james.love@boehringer-ingelheim.com
Cc: Varney, Deanne
Subject: IR re toxicities Afatinib

Jim,

Good Morning. Please ask your team to help me with the following and send me a reply before noon today.

Thanks

In pivotal study 1200.32

1) renal impairment as a consequence of diarrhea occurred in 6 .1% of patients treated with BRAND.
    a. Please grade them.
    b. Please confirm that none were fatal

Please confirm

2) ILD, occurred in 1.5% of more than 3800 patients (SAF %) who received BRAND across clinical trials of which (0.4%) percent were fatal and in pivotal study 1200.32 Grade ≥3 ILD events were experienced by 3 patients (1.3%) resulting in 2 deaths.

3) In 3800 patients who received BRAND across clinical trials, 10.1% of patients were reported with adverse events indicative of hepatic impairment of which 7 (0.18%) were fatal.

An adverse event indicative of hepatic impairment was reported in 17.5% of the patients treated with BRAND noted in ISS SAF1.

In CSR During treatment, approximately 10% of patients in the afatinib arm showed AST, ALT, or ALKP elevations ≥CTCAE Grade 2; the

Frequency of patients with values >CTCAE Grade 2 was below 3% for each of these parameters and AE's were apex 5%

Please Explain the disparities

Hepatic failure occurred in , including fatalities, has been reported during treatment with BRAND in less than 1% of patients (which data is this from? SAF 5?

4) Keratitis, occurred in (0.8%) of patients in SAF 5, Although 11 % have reported conjunctivitis have there been any reports indicative of Keratitis in 1200,32 study.

Shakun

APPEARS THIS WAY ON
ORIGINAL

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/s/

DEANNE R VARNEY
03/11/2013

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, February 27, 2013 3:01 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Nonclinical Information Request

Hello Ann,

Please see the below nonclinical information request for NDA 201292. Please provide a response by **COB on Tuesday, March 12, 2013.**

We note the submission of Study U07-1338-01: "BIBW 2992, an irreversible dual EGFR/HER2 kinase inhibitor, shows activity on L858R - and L858R/T790M-EGFR mutants." If you have conducted any additional studies investigating the specificity of afatinib on the inhibition of other EGFR mutations (e.g. exon 18 or 19 mutations) or any additional screening assays investigating the effects of afatinib inhibition on other kinases, please submit those studies to the NDA.

Please confirm receipt, and let me know if you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
02/27/2013

Varney, Deanne

From: Greeley, George
Sent: Monday, February 25, 2013 9:31 AM
To: Varney, Deanne
Cc: Berger, Mitchell (CBER); Suggs, Courtney
Subject: RE: New NDA 201292 - Full Pediatric Waiver Requested -PeRC Date --- Orphan Designation Received

Hi Deanne,

If you wanted to have this in DARRTS for this NDA it could only go in as a Memo To File. The pediatric page could be uploaded to DARRTS if this were a BLA but since it isn't you only have one choice in this instance if you have to have this in DARRTS.

Thanks,
George

From: Varney, Deanne
Sent: Friday, February 22, 2013 2:50 PM
To: Suggs, Courtney; Greeley, George
Cc: Berger, Mitchell (CBER)
Subject: RE: New NDA 201292 - Full Pediatric Waiver Requested -PeRC Date --- Orphan Designation Received

I have completed the pediatric page for afatinib. However, the only way to append my signature is in DARRTS ... but I know these don't need to checked in for orphan indications. Please let me know if you would like me to check it into DARRTS anyway in order to get a signature page, or if a signature page is not required.

<< File: NDA 201292 Pediatric Page.doc >>
Thank you,
Deanne

From: Suggs, Courtney
Sent: Friday, February 22, 2013 7:05 AM
To: Varney, Deanne; Greeley, George
Cc: Berger, Mitchell (CBER)
Subject: RE: New NDA 201292 - Full Pediatric Waiver Requested -PeRC Date --- Orphan Designation Received

Hi Deanne,

Since they received orphan designation they do not have to come to PeRC anymore. We will remove you from the calendar. Please submit a Peds Page to George and denote this.

Thanks,
Courtney

From: Varney, Deanne
Sent: Thursday, February 21, 2013 3:43 PM
To: Suggs, Courtney; Greeley, George

Subject: RE: New NDA 201292 - Full Pediatric Waiver Requested -PeRC Date --- Orphan Designation Received
Importance: High

Hi Courtney,

I have been alerted by the sponsor that afatinib received orphan designation for their proposed indication. Please see attached. As this exempts them from PREA requirements, will a PeRC meeting still be needed? And what documentation do you now need from me?

<< Message: NDA 201292_Afatinib Orphan Designation 12-3757 >>

Thanks,
Deanne

From: Suggs, Courtney
Sent: Tuesday, November 27, 2012 2:19 PM
To: Varney, Deanne; Greeley, George
Subject: RE: New NDA 201292 - Full Pediatric Waiver Requested -PeRC Date

Hi Deanne,

Afatinib is on the PeRC schedule for **March 27, 2013**. PeRC is usually held from 9 am to 12 am on Wednesdays. You will be notified of a specific time closer to the meeting date. Please send the completed documents covering ages birth to 16 years to be reviewed no later than **March 18, 2013**. Failure to do so will result in your product being rescheduled to a later date.

Please note that the templates in CDER Standard Letters (CSL) are not current so please be sure to use the forms on the PMHS website.

Here is the link to the PeRC information page where you will find the Pediatric Record and related templates:

http://wcms.fda.gov/InsideFDA/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/UCM027829.

The Pediatric Record (DARRTS) should reflect the opinions of the Division for each product and not merely those of the sponsor.

The Pediatric Plan submitted by the sponsor to support deferral requests MUST include a brief description of studies in addition to:
Protocol Submission Date
Study Completion Date
Final Report Submission Date

Thank you.

Courtney M. Suggs, Pharm.D., MPH
LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff

Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

From: Varney, Deanne
Sent: Tuesday, November 27, 2012 2:13 PM
To: Suggs, Courtney; Greeley, George
Subject: RE: New NDA 201292 - Full Pediatric Waiver Requested

Hi Courtney,

Thanks for your quick reply. The product is Afatinib and the PDUFA date is July 15, 2013.

Thank you,
Deanne

From: Suggs, Courtney
Sent: Tuesday, November 27, 2012 2:11 PM
To: Varney, Deanne; Greeley, George
Subject: RE: New NDA 201292 - Full Pediatric Waiver Requested

We need to get you on the PeRC calendar. What is the name of the product and the PDUFA date? NSCLC usually qualifies for an automatic full waiver so your Division probably won't have to attend PeRC in person. As part of the materials you will need to send to me for PeRC please include a pediatric record. I have attached instructions.

Courtney

<< File: Creating a Ped Record Report.doc >>

Courtney M. Suggs, Pharm.D., MPH
LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

From: Varney, Deanne
Sent: Tuesday, November 27, 2012 2:04 PM
To: Suggs, Courtney; Greeley, George
Subject: New NDA 201292 - Full Pediatric Waiver Requested

Hi Courtney and George,

A new NDA is in house for NSCLC and they have requested a full pediatric waiver because studies are impossible or highly impractical because the number of patients with NSCLC is so small. Is this a case where I am able to complete a pediatric record in DARRTS? If so, how to I access it? If not, I will complete the pediatric page and send to you.

Thank you,
Deanne

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/s/

DEANNE R VARNEY
06/28/2013

Varney, Deanne

From: Varney, Deanne
Sent: Friday, February 22, 2013 2:59 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Clinical Pharmacology Information Request

Hi Ann,

Please see the below clinical pharmacology information request. Please provide a response by COB on Friday, March 1, 2013.

As afatinib is a substrate and inhibitor of P-glycoprotein (P-gp) and also a BCRP inhibitor based on your in vitro test, the potential effects of afatinib on the pharmacokinetics (PK) of oral P-gp and BCRP probe substrates have not been addressed in this NDA submission. Please provide your plans to address this issue according to the FDA current draft drug-drug interaction guidance or provide your justification with data to support your determination that investigations of the effect of afatinib on the PK of P-gp and BCRP probe substrates are not warranted.

Please confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
02/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

INFORMATION REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor
Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afatinib tablets, 20 mg, 30 mg, 40 mg, (b) (4).

We also refer to your November 14, 2012 submission.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by March 4, 2013 in order to continue our evaluation of your NDA.

1. Clarify the discrepancy between Fig. 9 section 3.2.P.5.6 and Fig. 1.3. in section 2.7.1

2. Provide dissolution profiles using the proposed dissolution method, for the clinical batches used in the relative BA study 1200.35 (see table below).

Clinical protocol (description)	Dosage form	Strength [mg]	Drug product bulk batch number	Drug product batch size	Drug product manufacturing date	Drug product manufacturing site	Drug substance batch number	Formulation code (TF used)
1200.35 open label Phase I	Film-coated tablet	20	B071002217	(b) (4)	27.06.07	BIP GmbH&CoKG Biberach	06217	HU00134 (FF)
	Film-coated tablet	20	B071003953		06.11.07	BIP GmbH&CoKG Biberach	07137	HU00175 (FF)
	Film-coated tablet	20	B081002939		22.07.08	BIP GmbH&CoKG Biberach	07135	TAF 99 2A 1B (TF II)
	Film-coated tablet	20	808920		15.09.08	BIP GmbH&CoKG Ingelheim	2	70108 (FF)

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Ali H. Al Hakim
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
02/20/2013

TEAM MEETING MINUTES
February 6, 2013

New NDA 201292
Afatinib
Boehringer Ingelheim

Submission Date: November 14, 2012
Received Date: November 15, 2012
PDUFA Date: July 15, 2013
Early Target Action Date: June 5, 2013
Corresponding PMA Goal Date: June 5, 2013

Proposed Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test

Current Review Team for NDA 201292:
Patricia Keegan, Director DOP2
Deanne Varney, Regulatory Health Project Manager
Karen Jones (CPMS)
Shakun Malik, Medical Officer
Anthony Murgo, Medical Officer (CDTL)
Jonathan Norton, Statistics
Kun He, Statistics (TL)
Runyan Jin, Clinical Pharmacology
Jun Yang, Clinical Pharmacology
Hong Zhao, Clinical Pharmacology (TL)
Dubravka Kufrin, Non-Clinical
Whitney Helms, Non-Clinical (TL)
Li Shan Hsieh, Quality
Liang Zhou, Quality (TL)
Ali Al Hakim, Quality (TL)
Jewell Martin, Quality (ONDQA RPM)
Angelica Dorantes, Biopharmaceutics TL
Elsbeth Chikhale, Biopharmaceutics Reviewer
Rosane Charlab Orbach, Genomics Reviewer

Consults for NDA 201292:
James Schlick, OSE Proprietary Name Reviewer and DMEPA Reviewer
Todd Bridges, DMEPA TL
Bob Pratt, DRISK
Cynthia Lacivita, DRISK TL

Kate Coyle, DPV
Corrinne Kulick, DPV TL
Carol Broadnax, OPDP Professional Reviewer
Shenee Toombs, OPDP, Consumer Reviewer
Lauren Iacono-Connors, OSI
Tammy Brent-Howard, Maternal Health
Carrie Ceresa, Maternal Health TL
Karen Dowdy, PLT
Barbera Fuller, PLT (TL)
Adel Abou-Ali, DEPI

CDRH Review Team for PMA:
Jennifer Shen
Maria Chan

Review Status:

- Priority Review requested (PDUFA V --- 8 month review)
- Categorical Exclusion from environmental assessment requested
- Requested full waiver of pediatric studies, PeRC scheduled
- Requested waiver of half-page Highlights
- The clinical development of afatinib has been conducted under INDs 67969 and 114002.

Agenda Items:

1. **Discuss Target Action Date:** June vs. July

   Discussion: CDRH needs to ask Qiagen for additional information and will be sending the IR this week. CDRH will be putting Qiagen on hold during the first week in March, and the PMA clock will stop, so 6/5 will no longer be the action date. Qiagen will have 180 days to respond and can request an extension, but CDRH does not know when Qiagen will be able to respond. CDRH will ask for an estimated completion date from Qiagen.

   DOP2 will continue to target June 5th as an action date for the time being. Will need to discuss with Dr. Pazdur if this product might be approvable without the companion diagnostic approval.

2. **Milestone Goals Remaining:**

Milestone	8 month review July 15, 2013	6.5 month review June 5, 2013
Acknowledgment Letter	November 29, 2012 ***Issued November 20, 2012***	November 29, 2012 ***Issued November 20, 2012***

Priority Review Determination/Filing Issues Identified Letter	January 14, 2013 ***Issued January 11, 2013***	January 14, 2013 ***Issued January 11, 2013***
Mid-Cycle Communication	February 28, 2013 ***Scheduled February 20, 2013***	February 28, 2013 ***Scheduled February 20, 2013***
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	April 19, 2013	April 19, 2013
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	April 26, 2013	April 26, 2013
Issue Discipline Review Letters	April 26, 2013	April 26, 2013
Late Cycle Meeting Target Date	May 16, 2013	May 10, 2013
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 April 22, 2013 April 25, 2013 June 20, 2013 July 5, 2013 July 15, 2013	 April 22, 2013 April 25, 2013 May 11, 2013 May 26, 2013 June 5, 2013
Compile and circulate Action Letter and Action Package	June 25, 2013	May 16, 2013
FINAL Action Letter Due	**July 15, 2013**	**June 5, 2013**

Discussion: Late cycle meeting and labeling and PMC/PMR goals can remain the same regardless of goal date.

3. **Midcycle Preparations**: Any questions on presentations?

   Discussion: Ensure any PMC/PMR issues are highlighted.

4. **Reminder Regarding Midcycle Communication to BI on 2/20/13:**

   Discussion: The purpose of this call will be to update BI on:

- Any significant issues identified by the review team to date
- Any new information requests
- Information regarding major safety concerns
- Preliminary review team thinking regarding risk management
- Proposed date(s) for late-cycle meeting
- Updates regarding plans for the AC meeting
- Other projected milestone dates for the remainder of the review cycle

The RPM will confirm if the midcycle communication requires formal meeting minutes. Each discipline should send the RPM a list of the issues that require discussion in advance of the meeting (by February 15th).

Post-Meeting Note: Minutes from the midcycle communication must be sent to the applicant.

5. Review Issues: None discussed.

6. Inspections:

a. Clinical site inspections:

Tentative clinical site inspections schedule:
- Thailand Clinical Site: Mid-March
- Taiwan Clinical Site: Mid-March
- Germany Clinical Site: Mid-March
- CRO: Mid-Late March
- Sponsor/US: Early-Mid April (after site inspections)

Discussion: None.

b. Manufacturing site inspections - Most recent compliance status:

- Boehringer Ingelheim Pharma GmbH & Co. KG: Pending. Inspected 11/2012, initially OAI. Response currently under review with DIDQ, and their initial impression is "borderline"
- (b) (4) Pending; inspection date not yet provided
- (b) (4): Acceptable

Discussion: Major issue is the BI site. They are still under review for a warning letter, there is a possibility they will be downgraded to a VAI. Stability testing site scheduled for mid-March or April inspection.

7. Upcoming Internal Team Meetings:

i. **Mid-Cycle Meeting:** Scheduled for February 7, 2013.

ii. **Mid-Cycle Communication Sponsor Tcon:** Scheduled for February 20, 2013

iii. **Labeling Meetings (suggested section groupings):**

1. **March 7, 2013 Clinical & Stats**: Indications and Usage, Adverse Reactions, Warnings and Precautions, Contraindications, Overdosage

2. **March 13, 2013 Clinical & Stats**: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations

3. **March 21, 2013 CMC**: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling

   Include OSE during this labeling meeting to review carton and container

4. **March 27, 2013 Clin Pharm and Nonclinical**: Clinical Pharmacology and Nonclinical Toxicology

5. **April 3, 2012 Highlights, Patient Counseling Information**

6. **April 10, 2012: If needed**

7. **May 8, 2013: Discuss OPDP and/or applicant comments, if needed**

iv. **Monthly Team Meetings:**

1. January 10, 2013

2. February 6, 2013

3. March 6, 2013

4. April 8, 2013

5. May 20, 2013

6. June 5, 2013

7. July 3, 1013

v. **Wrap- Up Meeting**: May 6, 2013

vi. **Late Cycle Meeting with Applicant:** May 7, 2013

8. ODAC Not Needed

9. Consults/Collaborative Reviewers:

OPDP	Carole Broadnax - professional reviewer Karen Munoz - consumer reviewer Olga Salis – RPM
OSE	Sue Kang - OSE RPM Sean Bradley - OSE RPM TL *DMEPA to review carton/container and proprietary name review (request received 11/27/12) – James Schlick Todd Bridges – DMEPA TL DEPI: Adel Abou-Ali DRISK: Bob Pratt/Cynthia LaCivita DPV: Kate Coyle/ Corrinne Kulick
Maternal Health	Tammie Brent-Howard - Reviewer Carrie Ceresa – TL Melissa Tassinari
Facility/OMPQ	The sites have been entered in EES.
OSI	Lauren Iacono-Connors assigned, site selection in progress
Pediatric Page/PeRC	Full Waiver Requested ***PeRC scheduled March 27, 2013***
Patient Labeling Team	Karen Dowdy – Reviewer Barbara Fuller - TL
SEALD	*Consult sent 11/21/12*
QT-IRT	*Consult sent 12/3/12*
SGE's or Patient Representatives	Dr. Malik to work with (b) (4)

10. Miscellaneous Items or Issues?

- RPM to follow-up with DFO regarding any progress on SGE clearance

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/s/

DEANNE R VARNEY
02/06/2013

Varney, Deanne

From: Varney, Deanne
Sent: Monday, February 04, 2013 10:22 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Clinical/Statistical Information Request

Hi Ann,

Please see the below clinical/statistical information request. Please provide a response by **COB on Monday, February 18, 2013.**

The protocol for study 1200.32 states that patients will be followed every 60 days (+/- 15 days) until death. In the updated overall survival data sent on 1/28/2013, there were 33 patients who had a censoring date prior to 11/1/2012. In order to assess the benefit-risk profile of this product, FDA needs updated data on the vital status of these censored patients. We request that you use all practical methods, including checking appropriate public records, to provide either a death date or more recent censoring date (i.e., date last known alive) for each of these patients. We acknowledge that your ability to follow up on some patients may be limited by withdrawal of consent.

For study 1200.32, list which patients withdrew consent and state whether they refused further observation. Provide any available information about why each patient withdrew consent. If you are aware of any special circumstances in this study that would lead patients to withdraw consent, explain what they are.

For study 1200.32, confirm that 16/230 patients in the Afatinib arm were able to be dose escalated to 50 mg for 21 or more days, of whom 9 needed at least one dose reduction and 2 needed 2 dose reductions.

Please confirm receipt of this communication, and let me know should you have any questions.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
02/04/2013

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING DATE: January 28, 2013
TIME: 2:30 – 3:00 p.m. (EST)
LOCATION: WO 22 4311
APPLICATION: NDA 201292
DRUG NAME: (b) (4) (Afatinib)
TYPE OF MEETING: Proprietary name review teleconference

APPLICANT: Boehringer Ingelheim Pharmaceuticals, Inc.

MEETING CHAIR: Todd Bridges, Team Leader, DMEPA, OSE

MEETING RECORDER: Sue Kang, Safety Regulatory Project Manager, OSE

FDA ATTENDEES:

Todd Bridges, Team Leader, Safety Evaluator, DMEPA, OSE
James Schlick, Safety Evaluator, DMEPA, OSE
Sue Kang, Safety Regulatory Project Manager, OSE

APPLICANT ATTENDEES:

Joanne Palmisano, MD, Vice President, Regulatory Affairs
Thorsten Laux , PhD, Global Regulatory Affairs Manager
Pamela Strode, Executive Director, Regulatory Affairs
Ann Agnor, MS, Regulatory Affairs US
(b) (4)

Background:

DMEPA requested this teleconference to notify the applicant, Boehringer Ingelheim Pharmaceuticals, Inc., of their safety concerns with the proposed proprietary name, (b) (4) (request for name review dated November 26, 2012 and received November 27, 2012).

Discussion:

- DMEPA began the discussion by stating they have determined that the proposed proprietary name, (b) (4), is unacceptable (b) (4)
(b) (4)

(b) (4)

After DMEPA provided the (b) (4), the Applicant was provided an opportunity to comment. The following discussion points took place:

(b) (4)

Conclusion/Action Items:

- Applicant will withdraw Request for Proprietary Name Review submitted November 26, 2012 for (b) (4) under NDA 201292.
- Applicant will email OSE SRPM with three possible proprietary names for afatinib. DMEPA will take approximately three weeks to review and provide a

response regarding whether these three possible proprietary names for afatinib are likely to be acceptable or unacceptable.

- Applicant will submit their new proposed proprietary name to the NDA as an official submission after receiving feedback from FDA.

Call ended at 2:51 p.m. (EST)

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/s/

SUE H KANG
01/30/2013

TODD D BRIDGES
01/30/2013

Varney, Deanne

From: Varney, Deanne
Sent: Friday, January 25, 2013 10:25 AM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Another Statistical Information Request

Hi Ann,

Another statistical information request for you. Please provide a response by COB on January 30th.

In the report for study 1200.32, the links to "Appendix 16.2.6, Listing 1.1" and "Appendix 16.2.6, Listing 2.1" do not work. Provide this listing data in SAS transport format.

Please confirm receipt.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
01/25/2013

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, January 24, 2013 3:13 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Statistical Information Request

Hi Ann,

Please see the below statistical information request. Please provide a response by COB on January 30th, 2013.

For studies 1200.23 and 1200.32, submit any macros and formats needed to run the submitted SAS code which are not already in the EDR.

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
01/24/2013

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, January 23, 2013 4:28 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Information Request

Hi Ann,

Please confirm where each section of the label below will appear on the bottle. Specifically, we would like to know whether the quick response code will be on the principal display panel or the side panel.

Please confirm receipt of this communication, and let me know should you have any questions.

(b) (4)

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
01/23/2013

Varney, Deanne

From: Varney, Deanne
Sent: Friday, January 18, 2013 1:59 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Statistical Information Request

Hi Ann,

Please see the below information request from the statistics reviewer. Please provide a response by COB on Thursday, January 24th.

For study 1200.23, provide the charter for the Data Monitoring Committee. Also, state whether the committee has any access to unblinded data and, if so, describe what has been provided.

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
01/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

FILING COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor
Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Please refer to your New Drug Application (NDA) dated November 14, 2012, received November 15, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Afatinib tablets, 20 mg, 30 mg, 40 mg, (b) (4).

We also refer to your amendments dated November 26, 27, and 30, 2012, and January 03, 04 (2), and 08, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm. Therefore, the user fee goal date is **July 15, 2013**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 19, 2013. In addition, the planned date for our internal mid-cycle review meeting is February 7, 2013. A determination of the need for an advisory committee meeting to discuss this application has not yet been made.

During our filing review of your application, we identified the following potential review issues:

1. In Module 1.12.5, you state "Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) hereby requests a waiver from specific requirements outlined in 21 CFR 312.120 related to certain foreign clinical studies not conducted under an Investigational New Drug Application (IND), which came into effect February 28, 2007. In some cases, a trial/country is included in the waiver request pending a final evaluation for compliance."

   Please clarify the meaning of the second sentence, in particular, clarify the meaning of "pending a final evaluation for compliance."

2. The request for a waiver for foreign sites in Module 1.12.5 contains the following statement in Table 2: “Copies of case records and/or other medical records cannot be provided upon request. Direct access to original medical records as per ICH GCP (E6) 4.8.10(n) is permitted."

   Please clarify how you will meet the requirements of 21 CFR 314 in the event that we make requests for case records or other medical records at these study sites. In addition, provide clarification on the study sites affected, e.g., all sites in Table 1 identified by the superscript "a" or only a subset of these countries. If the latter, for each affected study, please identify the countries.

3. For study 1200.32, the description of the randomization method is lacking in detail. State what method was used, e.g., permuted block. If block randomization was used, then state the block size(s). Describe any adaptive features.

4. For study 1200.32, we note that you declined to provide the randomization scheme, stating, “This section is not applicable for the interim report as the randomisation lists are not archived in the CTMF until after Database Lock.” In order to appropriately review the study, we need sufficient information to assess whether the randomization was conducted as planned. The information needed may depend on the randomization method. If permuted block randomization was used, then submit a file that includes the subject ID, stratification factors, site, block number, and date/time of randomization.

5. The clinical study report for 1200.32 (p. 150) states “Type-2 error spending was managed across endpoints by pre-specifying a testing hierarchy.” We were not able to find a reference to this hierarchy in other documents. Provide a reference showing what the order of testing was and that it was appropriately pre-specified.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

During our preliminary review of your submitted labeling, we have identified the following labeling and labeling format issues:

6. Revise Figure 1 in Section 14.1 of the proposed labeling [redacted (b) (4)]

7. Remove data regarding [redacted (b) (4)] from Section 14 [redacted (b) (4)].

8. With regard to the description of study results for the LUX-2 trial in section 14.1 of the proposed labeling, provide data on the number of patients treated in the first- and second-line settings respectively and provide the duration of response for each subgroup. In addition, remove data [redacted (b) (4)] as the clinical relevance of these data cannot be interpreted in the context of a single-arm trial.

9. Section 12.6 is reserved for description of effects on cardiac electrophysiology; please renumber this section in the revised proposed labeling.

10. Section 17 of the package insert currently states [redacted (b) (4)] Please revise to state "See FDA-approved patient labeling (Patient Information)."

11. Section 17 of the package insert currently contains numbered subsections. Please remove these subsections and use bullet points instead.

We request that you resubmit labeling that addresses these issues by February 4, 2013. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the **Highlights** of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit

consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the PI and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Deanne Varney, Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

PATRICIA KEEGAN
01/11/2013

Varney, Deanne

To: Varney, Deanne
Subject: FW: Afatinib NDA 201292 - Information Request

From: Varney, Deanne
Sent: Tuesday, January 08, 2013 3:58 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Information Request

Hi Ann,

Please see the below information request for Afatinib NDA 201292. Please provide a response via email and as a formal submission to your NDA by **COB on Tuesday, January 15, 2013**.

Please confirm receipt of this message and let me know if you have any questions.

1. Please provide a bookmarked version of the blank case report form.

2. Please provide a subset of each site-specific individual subject data listings for the below 3 sites in PDF format:

   - Data listings organized by site for the following sites:

     3701 (Dr. Sarayut Lucien Geater)
     3601 (Prof. Yang, Chih-Hsin)
     4305 (Prof. Dr. med. Martin Schuler)

   - Site-specific individual subject data listings as follows (for the requested 3 sites):

     Randomization
     Protocol Deviations (Major and Minor)
     Demographic Data
     Individual Efficacy Response Data
     Adverse Events/Serious Adverse Events
     Listing of individual Laboratory Measurements
     Compliance and drug concentration data
     Con Meds
     Discontinued Subjects

     The data should be organized by site as illustrated here:

<< OLE Object: Picture (Device Independent Bitmap) >>

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
01/08/2013

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, December 20, 2012 3:22 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Clinical Pharmacology Information Request

Hello Ann,

Please see the below information request from the clinical pharmacology team.

Please provide your code and dataset (SAS transport file) used for exposure-response analyses for efficacy and safety (refer to Section 3.6 & 3.7 in the Summary of Clinical Pharmacology). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Please submit the above requested information to FDA **before January 5th, 2012.**

Please confirm receipt.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/20/2012

FILING MEETING MINUTES
December 13, 2012

New NDA 201292
Afatinib
Boehringer Ingelheim

Submission Date: November 14, 2012
Received Date: November 15, 2012
PDUFA Date: July 15, 2013
Corresponding PMA Goal Date: June 5, 2013

Proposed Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test

Current Review Team for NDA 201292:
Patricia Keegan, Director DOP2 --- ATTENDED
Deanne Varney, Regulatory Health Project Manager --- ATTENDED
Karen Jones (CPMS) --- ATTENDED
Shakun Malik, Medical Officer --- ATTENDED
Anthony Murgo, Medical Officer (CDTL) --- ATTENDED
Jonathan Norton, Statistics --- ATTENDED
Kun He, Statistics (TL) --- ATTENDED
Jun Yang, Clinical Pharmacology and Pharmacometrics --- ATTENDED
Runyan Jin, Clinical Pharmacology --- ATTENDED
Hong Zhao, Clinical Pharmacology (TL) --- ATTENDED
Nitin Mehrotra, Pharmacometrics (TL)
Dubravka Kufrin, Non-Clinical --- ATTENDED
Whitney Helms, Non-Clinical (TL) --- ATTENDED
Li Shan Hsieh, Product --- ATTENDED
Liang Zhou, Product (TL)
Chidambaram Nallaperum, Product (TL) --- ATTENDED
Jewell Martin, Product (ONDQA RPM) --- ATTENDED
Angelica Dorantes, Biopharmaceutics TL
Elsbeth Chikhale, Biopharmaceutics Reviewer --- ATTENDED

Consults for NDA 201292:
James Schlick, OSE Proprietary Name Reviewer and DMEPA Reviewer--- ATTENDED
Todd Bridges, DMEPA TL
Bob Pratt, DRISK
Cynthia Lacivita, DRISK TL
Kate Coyle, DPV--- ATTENDED

Corrinne Kulick, DPV TL
Carol Broadnax, OPDP Professional Reviewer
Karen Munoz, OPDP, Consumer Reviewer
Lauren Iacono-Connors, OSI
Tammy Brent-Howard, Maternal Health
Carrie Ceresa, Maternal Health TL
Karen Dowdy, PLT
Barbera Fuller, PLT (TL)
Adel Abou-Ali, DEPI

CDRH Review Team for PMA:
Nina Hunter--- ATTENDED
Yun-Fu Hu --- ATTENDED
Maria Chan

Additional Attendees:
Rick Pazdur
Haripada Sarker
Mahesh Ramanadham
Debasis Ghosh
Jeff Summers

Review Status:

- Priority Review requested (PDUFA V --- 8 month review)
- Categorical Exclusion from environmental assessment requested
- Requested full waiver of pediatric studies, PeRC scheduled
- Requested waiver of half-page Highlights
- The clinical development of afatinib has been conducted under INDs 67969 and 114002.

Agenda Items:

1. Filing Issues:

a. Clinical: No filing issues identified. An IR was sent requesting BI to identify where in the submission the rationale for assuming the applicability of foreign data is provided.

b. Statistics: No filing issues identified.

c. Clinical Pharmacology: No filing issues identified. A full clinical pharmacology package was provided.

d. CMC: No filing issues identified.

e. Nonclinical: No filing issues identified.

f. **Biopharmaceutics:** No filing issues identified.

g. **Regulatory:** No filing issues identified.

2. Inspections:

a. **Clinical site inspections** – The sites have been selected, scheduling is pending.

b. **Manufacturing site inspections** – A recent inspection of the following site lead to potential OAI status:

Boehringer Ingelheim
Pharma GmbH & Co. KG
FEI: 3002806556

3. Milestone Dates Reminder: 8-Month Priority Review Clock

Milestone	8 month review
Acknowledgment Letter	November 29, 2012 ***Issued November 20, 2012***
Priority Review Determination/Filing Determination Letter	January 14, 2013
Filing Issues Identified (74 Day Letter) --- if not sent in Day 60 letter	January 28, 2013
Mid-Cycle Communication	February 28, 2013
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	April 19, 2013
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	April 26, 2013
Late Cycle Meeting Target Date	May 5, 2013
Advisory Committee Target Date	May 16, 2013
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 April 22, 2013 April 25, 2013 June 20, 2013 July 5, 2013 July 15, 2013
Compile and circulate Action Letter and Action Package	June 25, 2013
FINAL Action Letter Due	**July 15, 2013**

4. Consults/Collaborative Reviewers:

OPDP	Carole Broadnax - professional reviewer Karen Munoz - consumer reviewer Olga Salis – RPM
OSE	Sue Kang/Frances Fahnbulleh - OSE RPM Sean Bradley - OSE RPM TL *DMEPA/CMC/OPDP to review carton/container, and patient labeling Proprietary Name Review (request received 11/27/12) – James Schlick DEPI: Adel Abou-Ali DMEPA: James Schlick/Todd Bridges DRISK: Bob Pratt/Cynthia LaCivita DPV: Kate Coyle/ Corrinne Kulick
Maternal Health	Tammie Brent-Howard - Reviewer Carrie Ceresa – TL Melissa Tassinari
Facility/OMPQ	The sites have been entered in EES.
OSI	Lauren Iacono-Connors assigned, site selection in progress
Pediatric Page/PeRC	Full Waiver Requested ***PeRC scheduled March 27, 2013***
Patient Labeling Team	Karen Dowdy – Reviewer Barbara Fuller - TL
SEALD	*Consult sent 11/21/12*
QT-IRT	*Consult sent 12/3/12*
SGE's or Patient Representatives	Dr. Malik to work with (b) (4)

4. Upcoming Internal Team Meetings:

i. **Mid-Cycle Meeting:** Scheduled for February 7, 2013.

ii. **Mid-Cycle Communication Sponsor Tcon:** Tentatively Scheduled for February 20, 2013

iii. **Labeling Meetings (suggested section groupings):**

1. **March 7, 2013 Clinical & Stats**: Indications and Usage, Adverse Reactions, Warnings and Precautions, Contraindications, Overdosage

2. **March 13, 2013 Clinical & Stats**: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations

3. **March 21, 2013 CMC**: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling

   Include OSE during this labeling meeting to review carton and container

4. **March 27, 2013 Clin Pharm and Nonclinical**: Clinical Pharmacology and Nonclinical Toxicology

5. **April 3, 2012 Highlights, Patient Counseling Information**

6. **April 10, 2012: If needed**

7. **May 8, 2013: Discuss OPDP and/or applicant comments, if needed**

iv. **Monthly Team Meetings:**

1. January 10, 2013

2. February 6, 2013

3. March 6, 2013

4. April 8, 2013

5. May 6, 2013

6. June 5, 2013

7. July 3, 1013

v. **Wrap- Up Meeting**: June 10, 2013

5. **Applicant Orientation Presentation:** Scheduled for December 14, 2012. During this meeting, we will request that BI submit their 120-day safety update by January 28th.

6. **ODAC Needed/Not Needed:** A determination will be made after review of the 120-day safety update.

   Target AC date: May 16, 2013

7. **Miscellaneous Items or Issues:**

   a. OSI inspections are needed. Site selection and scheduling in progress. Preclinical site audits are not required.

   b. CMC/Jewell Martin will assist with the following consults:
      - Establishment (EES)/Coordinate Inspections
      - Environmental Analysis: Request for Categorical Exclusion
      - Labeling

   c. Please ensure you have taken the Panorama 21st Century Reviewer/Team Leader Training: http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/Panorama/ucm319931.htm

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/s/

DEANNE R VARNEY
12/20/2012

Varney, Deanne

From: Varney, Deanne
Sent: Thursday, December 13, 2012 12:05 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: Afatinib NDA 201292 - Information Request

Hi Ann,

Please see below an information request from the clinical team. Please provide a response at your earliest convenience, and no later than 12PM on Friday, December 14th.

Have you submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? If so, please identify the file in the submission.

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
12/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292 **INFORMATION REQUEST**

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor
Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afatinib.

We also refer to your November 14, 2012, submission.

We are reviewing the chemistry, manufacturing and controls section of your submission and have the following comments and information requests. Please provide the following information by January 4, 2013, in order to continue our evaluation of your NDA:

1. Date of Letter of authorization (LoA) to reference DMF (b) (4)

2. Updated letter of authorization to reference DMF (b) (4), as provided letter is dated 10 July 2006.

3. A Certificate of analysis for the (b) (4) used in your drug product container/closure system.

4. The composition of the McIlvaine buffer pH 4.0.

5. Dissolution method development report with complete detailed information supporting the selection of this method for the evaluation of dissolution characteristics of Afatinib tablets.

   The dissolution method development report should include the following information:
   a. Solubility data for each drug substance covering the pH range;
   b. Detailed description of the dissolution test being proposed for evaluation of your proposed drug product and the developmental parameters used to select the proposed dissolution method as the optimal test for the proposed product (*i.e., selection of the equipment/ apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.*). Include data to support the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The

dissolution profile should be complete (*i.e., 15, 20, 30, 45, & 60 minutes*) and cover at least (b) (4) of drug release of the labeled amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend that at least twelve samples be used per testing variable;

c. Provide complete dissolution profile data (*individual, mean, SD, profiles*). The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and
d. Include complete dissolution data for the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

For the setting of dissolution acceptance criterion for your product, the following points should be considered:

e. The dissolution profile data (*i.e., 10, 15, 20, 30, 45, & 60 minutes*) from the clinical batches and primary (registration) stability batches should be used for the setting of dissolution acceptance criteria.
f. The in vitro dissolution profile should encompass the timeframe over which at least (b) (4) of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
g. The selection of the specification time point should be where Q = (b) (4) dissolution occurs.
h. The dissolution acceptance criterion should be based on average dissolution data (n=12).

Note that the final determination on the acceptability of your proposed acceptance criterion for your product will be made during NDA review process based on provided data.

6. The dissolution data that you collect during your stability study should cover the complete dissolution profile (*i.e., 10, 15, 20, 30, 45, & 60 minutes*). Please provide these data. If you have not collected these dissolution data at all appropriate time points, you should start collecting these data for the remaining stability time points and submit to your NDA.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Nallaperumal Chidambaram, PhD
Acting Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NALLAPERUM CHIDAMBARAM
12/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: November 30, 2012

FROM: Patricia Keegan, M.D.,
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products

SUBJECT: Designation of Priority for NDA Review
Sponsor: Boehringer Ingelheim
Product: Afatinib
Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor inhibitor (EGFR) mutation(s).

TO: NDA 201292

The review status of this file is designated to be:

□ Standard (12 mon.) ✓ Priority (8 mon.)

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

DEANNE R VARNEY
11/30/2012

PATRICIA KEEGAN
01/04/2013

Varney, Deanne

From: Varney, Deanne
Sent: Wednesday, November 28, 2012 12:50 PM
To: ann.agnor@boehringer-ingelheim.com
Subject: NDA 201292 Information Request

Hello Ann,

We have the following clinical information request for NDA 201292. Please provide a response via email by COB on Thursday, November 29th. Once the email response is received, I will let you know if a formal amendment to the NDA is required as well.

- Please identify the "Independent Review Charter" in the NDA. Appendix 16.1.9.7, referred to on Page 36 of the Study Report for Pivotal Trial 1200.32, cannot be located.

Please confirm receipt of this communication.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
11/28/2012

PLANNING MEETING MINUTES
November 28, 2012

New NDA 201292
Afatinib
Boehringer Ingelheim

Submission Date: November 14, 2012
Received Date: November 15, 2012

Proposed Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test

Current Review Team for NDA 201292:
Patricia Keegan, Director DOP2 --- ATTENDED
Deanne Varney, Regulatory Health Project Manager --- ATTENDED
Karen Jones (CPMS) --- ATTENDED
Shakun Malik, Medical Officer --- ATTENDED
John Johnson, Medical Officer (TL and CDTL) --- ATTENDED
Jonathan Norton, Statistics --- ATTENDED
Kun He, Statistics (TL) --- ATTENDED
Jun Yang, Clinical Pharmacology --- ATTENDED
Hong Zhao, Clinical Pharmacology (TL) --- ATTENDED
Dubravka Kufrin, Non-Clinical --- ATTENDED
Whitney Helms, Non-Clinical (TL) --- ATTENDED
Li Shan Hsieh, Product --- ATTENDED
Liang Zhou, Product (TL)
Chidambaram Nallaperum, Product (TL) --- ATTENDED
Jewell Martin, Product (ONDQA RPM) --- ATTENDED
Angelica Dorantes, Biopharmaceutics TL
Elsbeth Chikhale, Biopharmaceutics Reviewer --- ATTENDED

Additional Attendees:
Lauren Iacono-Connors
Tammy Brent-Howard
Anthony Murgo
Jeff Summers
Hari Sarker
John Leighton

CDRH Review Team for PMA:
Nina Hunter

Donna Roscoe
Maria Chan

Agenda Items and Discussion:

1. Review Status:

- Priority Review requested (PDUFA V --- 8 month review)
- User Fee Paid
- Categorical Exclusion from environmental assessment requested
- Requested full waiver of pediatric studies
- Requested waiver of half-page Highlights
- The clinical development of afatinib has been conducted under INDs 67969 and 114002.

DISCUSSION: Priority review will most likely be granted. PeRC has been scheduled for March 27, 2012. RPM will send pediatric waiver information to PeRC. All PMR/PMC information should be submitted to IND 114002. RPM to distribute all pre-NDA meeting minutes to the team.

2. Milestone Dates: 8-Month Priority Review Clock

Milestone	8 month review
Acknowledgment Letter	November 29, 2012 ***Issued November 20, 2012***
Priority Review Determination/Filing Determination Letter	January 14, 2013
Filing Issues Identified (74 Day Letter) --- if not sent in Day 60 letter	January 28, 2013
Mid-Cycle Communication	February 28, 2013
Send proposed labeling/PMR/PMC/REMS to applicant (Target Date)	April 19, 2013
Week after the proposed labeling has been sent, discuss the Labeling/PMR/PMC with Applicant	April 26, 2013
Late Cycle Meeting Target Date	May 5, 2013
Advisory Committee Target Date	May 16, 2013
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 April 22, 2013 April 25, 2013 June 20, 2013 July 5, 2013 July 15, 2013
Compile and circulate Action Letter and Action Package	June 25, 2013
FINAL Action Letter Due	**July 15, 2013**

DISCUSSION: One potential filing issue was discussed, concerning the potential lack of preferred AE terms. The clinical team will work with Dr. Summers to determine if preferred terms were provided. If it is not clear, a teleconference will be arranged with the Applicant.

It was mentioned that the majority of the patients are from outside the United States, and two thirds are Asian. It was noted that this is not a filing issue, but the Applicant should provide justification. A comment can be included in the 74-day letter.

It was also noted that the overall survival data is not mature. The team will review the pre-NDA agreements to see if this was previously discussed and agreed to.

3. Potential Consults/Collaborative Reviewers Needed:

OPDP	*Consult sent 11/21/12* Carole Broadnax - professional reviewer Karen Munoz - consumer reviewer Olga Salis – RPM
OSE	*Consult sent 11/21/12* Sue Kang/Frances Fahnbulleh - OSE RPM Sean Bradley - OSE RPM TL *DMEPA/CMC/OPDP to review carton/container, and patient labeling Proprietary Name Review (request received 11/27/12) – James Schlick DMEPA: Not yet assigned DRISK: Not yet assigned DPV: Not yet assigned
Maternal Health	*Consult sent 11/21/12* Tammie Brent-Howard - Reviewer Carrie Ceresa – TL Melissa Tassinari
Facility/OMPQ	The sites have been entered in EES.
OSI	*Consult needed* Lauren Iacono-Connors assigned, need to

	select sites.
Pediatric Page/PeRC	Full Waiver Requested ***PeRC scheduled March 27, 2013***
Patient Labeling Team	*Consult sent 11/21/12* Karen Dowdy – Reviewer Barbara Fuller - TL
SEALD	*Consult sent 11/21/12*
SGE's or Patient Representatives	Dr. Johnson to work with (b) (4)

DISCUSSION: The team reviewed and discussed consults already requested and those remaining to be assigned. The pediatric waiver discussion for this application will be held on March 27, 2013. The CMC/facility team will provide a date for site inspection at the filing meeting.

4. Upcoming/TBD Internal Team Meetings:

- **Filing Meeting:** Scheduled for December 13, 2012.

  a. Please be prepared to identify significant filing issues for day 74 letter. The template is available on the 21st Century website. http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/21stCenturyReview/ucm034190.htm

  DISCUSSION: Reminder was given to the team to bring their draft filing memos to the filing meeting; all filing review memos must be signed-off in DARRTs prior to the January 14, 2013, filing date.

- **Mid-Cycle Meeting:** Scheduled for February 7, 2013.

  DISCUSSION: No discussion.

- **Mid-Cycle Communication Sponsor Tcon:** Tentatively Scheduled for February 20, 2013

  DISCUSSION: No discussion.

- **Labeling Meetings (suggested section groupings):**

  a. _____(Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions, Contraindications, Overdosage)
  b. _____ (Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations)

  c. _____ (CMC: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling)
  ******Include OSE/CMC during this labeling meeting to review carton and container.

  d. _____ (Clin Pharm and Nonclinical Sections: Clinical Pharmacology and Nonclinical Toxicology)

  e. _____ (Highlights, Patient Counseling Information)

  DISCUSSION: The team agreed to begin labeling meetings after the mid-cycle meeting, at the end of February or early March. The RPM will set up 5 labeling meetings and will identify which sections will be reviewed during the meeting and who will be required to attend.

- **Team Meetings and PMR/PMC Working Meetings**:
  - Do we want to schedule monthly team meetings?
  - Do we want to schedule separate PMC/PMR meetings?

  DISCUSSION: Monthly team meetings will be scheduled. The RPM will determine if OIVD would like to attend the monthly team meetings or if they would prefer separate meetings with only clinical and statistics.

  The PMR/PMC development templates should be finalized no later than June 25, 2013. A tentative PMR/PMC meeting will be scheduled.

- **Wrap- Up Meeting**: TBD, By June 11, 2013.

  DISCUSSION: No discussion occurred.

5. **Applicant Orientation Presentation:** Scheduled for December 14, 2012.

   DISCUSSION: No discussion occurred.

6. ODAC Needed/Not Needed:

Target AC date: May 16, 2013

If not needed, for an original NME or BLA application, include the reason in the RPM filing review memo. For example:

- *this drug/biologic is not the first in its class*
- *the clinical study design was acceptable*
- *the application did not raise significant safety or efficacy issues*
- *the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*

If we plan on going to Advisory Committee, we will need a planning meeting and _____ practice sessions.

DISCUSSION: The team will determine at a later date if an AC is needed.

7. Miscellaneous Items or Issues:

a. OSI inspections are needed.

b. CMC/Jewell Martin will assist with the following consults:
- Establishment (EES)/Coordinate Inspections
- Environmental Analysis: Request for Categorical Exclusion
- Labeling

c. Please ensure you have taken the Panorama 21st Century Reviewer/Team Leader Training: http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/Panorama/ucm319931.htm

DISCUSSION: The clinical reviewer is working with OSI to select clinical sites for inspection.

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/s/

DEANNE R VARNEY
11/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

NDA ACKNOWLEDGMENT

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor
Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Afatinib tablets, 20 mg, 30 mg, 40 mg, (b) (4)

Date of Application: November 14, 2012

Date of Receipt: November 15, 2012

Our Reference Number: NDA 201292

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **January 14, 2013**, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Deanne Varney, Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN D JONES
11/20/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

MEETING REQUEST GRANTED

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor
Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afatinib.

We also refer to your November 14, 2012, correspondence requesting an application orientation meeting.

The meeting is scheduled as follows:

Date: Friday, December 14, 2012
Time: 1:00PM – 2:00PM EST
Location: 10903 New Hampshire Avenue
White Oak Building 22
Silver Spring, Maryland 20903

FDA participants:
Richard Pazdur
Patricia Keegan
Shakun Malik
John Johnson
Deanne Varney
Jonathan Norton
Kun He
Jun Yang
Hong Zhao
Dubravka Kufrin
Whitney Helms
Li Shan Hsieh
Nallaperum Chidambaram
Jeff Summers

Please e-mail me your attendee list at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with the following number to request an escort to the conference room: Deanne Varney, 301-796-0297

If you have any questions, call me at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	Boehringer Ingelheim
MEETING START DATE AND TIME	December 14, 2012, 1PM
MEETING ENDING DATE AND TIME	December 14, 2012 2PM
PURPOSE OF MEETING	Application Orientation
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	Building 22
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	Deanne Varney, RPM, 22/5235, 6-0297
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

DEANNE R VARNEY
11/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 10, 2012

From: Deanne Varney, RPM DOP2/OHOP/CDER/FDA

Subject: IND 114002/Pre-Assigned NDA 201292

TELECONFERNCE

Sponsor Attendees:

Boehringer Ingelheim

Christian Meissner	R&D Project Manager
Dennis O'Brien	Director, Team Member, Drug Safety
Ellen Gold	Executive Director, Global Safety Evaluation, Oncology
Victoria Zazulina	Team Member Medicine, Oncology
Vikram Chand	Team Member Medicine, Oncology
James Love	Project Statistician
Julie Cong	Project Statistician
Sven Wind	Project Pharmacokineticist
Sabine Luik	Sr. Vice President, Medicine & Regulatory Affairs, US Regional Medical Director, North America
Joanne Palmisano	Vice President, Regulatory Affairs
Pamela Strode	Executive Director, Regulatory Affairs
David Jones	Regulatory Area Lead, Oncology
Jim Segretario	Director, CMC Regulatory Affairs
Ann Agnor	Associate Director, Regulatory Affairs

FDA Attendees:

Deanne Varney	Regulatory Project Manager, DOP2
Patricia Keegan	Director, DOP2
John Johnson	Clinical Team Leader, DOP2
Hong Zhao	Clinical Pharmacology Team Leader, DOP2
Whitney Helms	Pharmacology/Toxicology Team Leader, DHOT
Li Shan Hsieh	CMC Reviewer, ONDQA
Janet Jiang	Statistical Reviewer, DBV

Objectives:

Discuss contents of a complete application, in accordance with PDUFA V, for the planned NDA submission of November 2, 2012. The discussion included agreement on content of the application upon submission, agreement on whether FDA would accept for submission a limited number of minor components within 30 days of the original submission, and discussion of the need for a REMS.

Discussion:

1. The content of the application was discussed. FDA confirmed receipt and review of the draft Table of Contents from BI, and discussed the following issues and questions:

   a. BI was informed that everything must be submitted electronically to the NDA; specifically cross-references to information contained in the paper IND file will not be acceptable. BI confirmed their understanding of this.

   b. BI confirmed that the labeling would be submitted in SPL format, Word format, and as annotated PDFs with hyperlinks. BI also confirmed that the labeling will follow all of the appropriate FDA guidance documents.

   c. It was confirmed that at this time, FDA has not identified the need for a proposed REMS for Afatinib.

   d. FDA inquired into the contents of the efficacy and safety datasets. BI confirmed that all data will be provided in CDISK and in SAS datasets; BI clarified that the datasets are derived from the eCRF. Specifically, analysis datasets (ADS) will be traceable to the Oracle Clinical source data. However, the analysis datasets will not be directly linked to the Case Report Tabulations in SDTM format, which were not used as the source of the analysis datasets. FDA requested that safety data presented in summary format be generated from a single dataset, such that FDA would not need to merge the data. FDA inquired as to whether safety data for an individual study will be provided for each of the four clinical studies. BI requested a follow-up discussion off-line to ensure adequate understanding of this inquiry, but stated that they will provide a proposal for FDA review during the week of October 15, 2012.

   e. FDA stated that all versions of the study protocol and amendments for each study in the NDA should be included in the NDA submission. BI confirmed their understanding.

   f. FDA stated that the Statistical Analysis Plan (SAP) and all amendments to the SAP for each study in the NDA supporting safety and efficacy should be included in the NDA submission. BI confirmed their understanding.

   g. FDA stated that appropriate references for novel statistical methodology should be included if the method was used. BI stated that no novel methodologies have been used.

   h. FDA stated that if there was any pre-specified interim analysis conducted or reviewed by an independent Data Safety Monitoring Board (DSMB)/ Data Monitoring Committee (DMC), DSMB/DMC meeting minutes and data should be submitted. BI confirmed their understanding.

   i. FDA stated that on page 54-57 in document 1200-0032-analysis reviewers-guide.pdf, there are more than 60 tables and figures created by SAS program pfs.sas. Since SAS programs and macros generated by BI may be the BI system-

dependent, BI suggested that these programs/macros may not function as stand-alone programs and agreed to submit alternative SAS programs capable of running without proprietary BI technology to reproduce the major efficacy and safety results in the Clinical Study Report and the proposed labeling. FDA also requested that BI provide a document (.pdf) that provides descriptions of analyses, the names of datasets and variables used in these alternative SAS programs. BI confirmed their understanding, but requested a follow-up discussion off-line to ensure adequate understanding of this request.

j. FDA asked BI if any renal impairment studies were conducted. BI stated that no dedicated renal impairment studies have been conducted but that the issue has been addressed by a population pharmacokinetic analysis. FDA noted that it will be a review issue to determine if the effect of renal impairment on afatinib pharmacokinetics has been adequately addressed.

k. FDA reiterated that all studies must be submitted to the NDA in electronic format, including older nonclinical study reports previously submitted to the IND, and that if scanned documents are provided they must be high-quality, legible scans.

2. It was confirmed that no application components will be submitted late.

3. FDA reminded BI that all applications are expected to be complete at the time of original submission and are expected to include a comprehensive list of all clinical sites and manufacturing facilities. BI confirmed their understanding of this.

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/s/

DEANNE R VARNEY
10/16/2012

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	December 9, 2011 3:00 pm
Meeting Location:	WO 22 Rm 1315
Application Number:	IND 067969
Product Name:	Afatinib (BIBW 2992)
Indication:	Non-Small Cell Lung Cancer
Sponsor/Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Meeting Request Date:	September 9, 2011
Meeting BGP date:	November 4, 2011
Meeting Chair:	Virginia Maher, M.D., Clinical Team Leader
Meeting Recorder:	Amy Tilley, Regulatory Project Manager

FDA ATTENDEES

Robert Justice, M.D., M.S., Director DOP1
Anthony Murgo, M.D., M.S., FACP, Associate Director IO/OHOP
Amna Ibrahim, M.D., Deputy Division Director, DOP1
John R. Johnson, M.D., Clinical Team Leader
Virginia Maher, M.D., Clinical Team Leader
Geoffrey Kim, M.D., Medical Officer
Shakun Malik, M.D., Medical Officer
Anne M. Pilaro, Ph.D., Supervisory Toxicologist
Shenghui Tang, Ph.D., Team Leader, DB 5
Somesh Chattopadhyay, Ph.D., Mathematical Statistician, DB 5
Robert Becker, M.D., Chief Medical Officer, OIVD/CDRH
Reena Philip, Ph.D., Deputy Director, DIHD/OIVD/CDRH
Timothy Schaefer, Ph.D., Scientific Reviewer, OIVD/CDRH
Amy Tilley, Regulatory Project Manager

SPONSOR ATTENDEES

Mehdi Shahidi, M.D., Global Clinical Programme Team Leader
Robert Lorence, M.D., Ph.D., Senior Director, Clinical Research, Oncology
Pamela Strode, Executive Director
Robin Christoforides, MS, Senior Associate Director
Thorsten Laux, Ph.D., International Project Team Member DRA
Dennis O'Brien, M.D., Director, Team Member Drug Safety
Kirsten Herbach, Ph.D., Team Leader Medical Writing Europe
Rainer Kleemann, Dr. Med. Vet., International Project Leader
James Love, M. Stat., Project Statistician
Julie Cong, Ph.D., Project Statistician
Yimei Wang, MS, Associate Director, Statistical Programming

1.0 BACKGROUND

Afatinib is a small molecule kinase inhibitor with activity against the epidermal growth factor receptors 1 and 2 (EGFR and HER-2 respectively). To date, over 3700 patients have been treated with afatinib in a wide variety of disease settings, particularly non small cell lung cancer, breast cancer, head and neck squamous cell carcinoma, and glioblastoma. In this pre-NDA meeting, the sponsor has proposed a NDA package containing 1200.32 (pivotal) and 1200.22, 1200.23, and 1200.42 (3 supportive trials). The sponsor was provided with a SPA non-agreement letter on April 14, 2009 for the 1200.32/LUX-Lung 3 protocol; A randomized open-label, multicenter, phase 3 study of BIBW 2992 vs. chemotherapy as first-line therapy for patients with Stage IIIB or IV adenocarcinoma of the lung harboring an EGFR activating mutation. Comments to the sponsor regarding the use of PFS as the primary endpoint were conveyed to the sponsor with the letter. The sponsor anticipates results from the LUX-Lung 3 trial at the end of the first quarter of 2012 and wishes to discuss:

- The sponsor's strategy to support the proposed indication.
- The information and presentation of the clinical and safety data, including clinical pharmacology, to be submitted in the NDA and 4-month safety update report to support the proposed indication.

2.0 DISCUSSION

CLINICAL RATIONALE / SUBMISSION STRATEGY TO SUPPORT PROPOSED INDICATION

QUESTION 1:

As discussed in Section 13, does the Agency agree with BI's proposed clinical rationale and submission strategy to submit the results from the pivotal and supportive trials to provide an adequate basis for assessing the efficacy and safety in patients with NSCLC with EGFR mutations regardless of the line of treatment?

FDA Response:

The indication will be a review issue and should reflect the patient population enrolled in the trials. We remind you that the diagnostic test kit must be approved at the time of the NDA approval.

We reiterate our comment regarding the primary endpoint of progression free survival that was included in the SPA Non-Agreement letter sent in April 2009: "…whether PFS is acceptable as the primary endpoint will be a review issue. In general, a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision making…"

BI Response:

BI acknowledges that the therascreen EGFR RGQ PCR Kit (subject to Pre-IDE I080206) must be approved at the time of the NDA approval. BI plans to submit the afatinib NDA submission in late August 2012 at which time we plan to request a priority review. Please note, Qiagen plans to submit the PMA for the therascreen EGFR RGQ PCR Kit in early September 2012.

Meeting Discussion:

FDA can not state whether submission of the PMA is a filing issue. However, both the test kit and drug, if approved, should both be approved simultaneously.

MODULE 2 SUMMARIES

QUESTION 2:

As discussed in Section 13, BI plans to include the results of four studies (1200.32, 1200.22, 1200.23 and 1200.42) in the NDA to support the proposed indication (see Section 3). The data from these studies will be presented separately. Due to the different study designs and/or patient populations, a pooled analysis of efficacy data would not be meaningful. Therefore, BI does not plan to pool the data from the four trials – See Section 3.3 of APPENDIX 2 for details on the proposed structure and content of the Summary of Clinical Efficacy (SCE).

In accordance with the Guidance for Industry entitled, "Integrated Summary of Effectiveness (ISE) [April 2009]", BI will address all of the context requirements of an ISE in Section 2.7.3 (Summary of Clinical Efficacy, SCE). All analyses that are required for an ISE will be performed as part of the Clinical Trial Reports of the four studies, which will include the detailed statistical analysis results and listings of derived data used in the analysis as appendices. The Clinical Trial Report analyses will also be used as the source data for the SCE. However, if additional analyses become necessary that cannot be included in the Clinical Trial Reports, these will be placed in a separate report in Module 5.3.5.3. Based on the above BI does not believe that it is necessary to provide a specific ISE in Module 5.3.5.3.

Does the Agency agree with the proposed strategy for the evaluation and presentation of clinical efficacy data?

FDA Response:

Yes, the proposed strategy appears acceptable. However, you should also include the efficacy outcomes, as available, from the following studies in NSCLC: 1200.33, 1200.34, 1200.40, 1200.41, and 1200.72.

BI Response:

BI plans to include in the NDA submission Clinical Trial Reports for trials 1200.33 (Phase I and Phase II), and 1200.72. Clinical Trial Reports for trials 1200.40, 1200.41, and 1200.34 will not

be available at the time of submission. Study 1200.40 has just recently completed recruitment and last patient out is expected to occur in July 2012. According to BI SOPs, the final Clinical Trial Report would be anticipated to be available in November 2012. The current enrollment in Study 1200.41 substantially lags behind planned timelines, the trial is still ongoing, and a Clinical Trial Report would not be available at the time of the NDA submission. As per BI SOPs, Study 1200.34 is handled internally as if it was a double-blind trial. Since no interim analysis is planned for 1200.34, BI does not plan to provide any efficacy outcome data for 1200.34 at the time of the NDA submission. BI proposes to summarize in the SCE the efficacy outcomes of trials 1200.33 (Phase II) and 1200.72.

Does the Agency agree with BI's proposal?

Meeting Discussion:

The sponsor's plan is acceptable. The sponsor will provide safety data from all 5 trials and will provide efficacy data from 1200.33 and 1200.72 in the SCE.

QUESTION 3:

The grouping of safety studies, the proposed combined safety analyses, and the structure and content of the Summary of Clinical Safety (SCS, Section 2.7.4) are described in Section 4 of APPENDIX 2. BI believes that Module 2.7.4 (Summary of Clinical Safety, SCS) coupled with supportive tables, figures, and listings in Module 5.3.5.3 constitutes an adequate Integrated Summary of Safety (ISS).

Does the Agency agree with the proposed strategy for the evaluation and presentation of clinical safety data?

FDA Response:

Yes, the proposed strategy appears acceptable. Please include Study Number, Dose, and SAF stratum in your integrated adverse event dataset.

BI Response:

BI agrees to include in the NDA submission the Study Number, Dose, and SAF stratum in the integrated adverse event dataset.

Meeting Discussion:

None

MODULE 5 – CLINICAL

Patient Narratives

QUESTION 4:

In accordance with the ICH Guideline for Industry entitled, "Structure and Content of Clinical Study Reports", BI is planning to provide patient narratives for the following events while on treatment and those reported after the 28 day post-treatment follow-up, with the exceptions noted:

a) Only deaths of afatinib-treated patients with the exception of those deaths due to progression of underlying disease determined by medical review and considered not related to afatinib.
b) Only related other serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths).
c) Only related adverse events that led to the permanent discontinuation of afatinib.

In addition, narratives for the following other significant adverse events will be provided for all events "while on treatment" and for only related events reported after the 28 day post-treatment follow-up:

a) Patients with interstitial lung disease-like events.
b) Patients with cardiac failure events, including patients with a decrease in left ventricular ejection fraction (LVEF) which is equal to or greater than 20% from baseline and below the institution's lower limit of normal. If the institution's lower limit of normal is not known, a lower limit of normal value of 50% will be used.

Note: Events reported "while on treatment" includes the post-treatment follow-up period of 28 days. The post-treatment follow-up period was not consistentlydefined across protocols. For the purpose of the NDA submission, BI will use the period of 28 days as noted above, regardless of the "follow-up period" defined in the individual trials.

BI believes that in order to provide an accurate medical review for the NDA, separate narratives should be provided for those patients who participated in any trial for which a Clinical Trial Report (i.e., completed study) or Interim Report (i.e., ongoing study) has been provided in the original NDA submission and meet the criteria noted above.

BI anticipates that the 4-month Safety Update Report will include new Clinical Trial Reports that become available prior to the safety update report cut-off date. For these new Clinical Trial Reports, BI does not plan to provide separate patient narratives in the 4-month Safety Update Report. However, narratives will be provided in the Clinical Trial Report in Section 15.4.3 as CIOMS forms. In addition, BI does not plan to provide updated or new patient narratives for patients that continue therapy after the NDA cut-off date (i.e. report date), except for those in studies 1200.22, 1200.23, 1200.32 and 1200.42.

The narratives will take into account all available information on the respective patient, will be medically reviewed, and will include a medical assessment. The event terms will be coded using MedDRA Version 14.1.

Does the Agency agree with BI's proposal described above?

FDA Response:

No. Narratives should be provided for all patients who died due to an adverse event while on treatment and during the 28-day post-treatment follow-up period. Narratives should also be provided for 1) Interstitial lung disease like events; 2) Decreased LVEF/Heart Failure events; 3) Hepatic Failure events; and 4) AEs leading to discontinuation. These should be provided regardless of their relationship to study drug. It is acceptable to provide narratives only for serious adverse events which occurred during the treatment period (+28 days) and which are at least possibly related to study drug. However, you should be prepared to provide narratives for additional adverse events upon request.

BI Response:

Please clarify if the request to provide "all patients" means all afatinib-treated patients or all treated patients regardless of treatment (i.e. afatinib and control).

BI agrees to provide patient narratives for Interstitial lung disease like events, Decreased LVEF/Heart Failure events and Hepatic Failure events regardless of their relationship to study drug.

BI agrees to provide patient narratives in the NDA submission for all patients who had an AE leading to death regardless of relationship to study drug. Please note, clinical trial protocols required reporting of signs and symptoms of disease progression as adverse events. Furthermore, disease progression itself has been reported as an adverse event in some cases. Therefore, a large number of adverse events leading to death clearly represent disease progression. BI proposes to exclude narratives when the reported term describes disease progression (that is, the investigator reports disease progression, the underlying malignancy, or metastasis as an event). This would also apply to AEs leading to discontinuation.

Does the Agency agree with BI's proposal?

Meeting Discussion:

For studies 1200.32, 1200.22, 1200.23, and 1200.42:

FDA clarified that the sponsor should provide narratives for all deaths attributed to an adverse event in any study arm on the NSCLC trials. It is not necessary to provide narratives for deaths attributed to progressive disease. However, these should be available upon request. Narratives for adverse events leading to discontinuation and serious adverse events should be provided for events which are at least possibly attributable to study drug.

For other studies:

Narratives should be provided for 1) Interstitial lung disease like events; 2) Decreased LVEF/Heart Failure events; 3) Hepatic Failure events for patients on afatinib.

Case Report Form(s)

QUESTION 5:

In accordance with 21 CFR 314.50(f)(2), BI is planning to provide CRFs for studies 1200.32, 1200.22, 1200.23, and 1200.42 for each patient who died or who did not complete the study because of an adverse event, whether believed to be drug-related or not, including patients receiving afatinib or placebo or comparator and for each patient with a serious adverse event (SAE) while on treatment and post-treatment follow-up period of 28 days.

For all other studies that will be included in the NDA and 4-month Safety Update Report, BI does not plan to provide CRFs for the review of the NDA as the majority of patients in these studies represent different patient populations.

Does the Agency agree?

FDA Response:

No. You should provide case report forms for all deaths during the treatment period (+28 days), discontinuations, and related serious adverse events that are included in the 4 month Safety Update.

BI Response:

BI agrees to provide case report forms for all deaths during the treatment period (+28 days), discontinuations, and related serious adverse events that are included in the 4-month Safety Update for studies 1200.32, 1200.22, 1200.23, and 1200.42.

Please clarify if BI's original proposal for the NDA submission is adequate.

Meeting Discussion:

The sponsor's plan is acceptable.

QUESTION 6:

Electronic data capture (EDC) was used for studies 1200.32, 1200.22, 1200.23 and 1200.42 to capture subject information by investigators. BI plans to provide individual subject's completed CRFs as separate PDF files in the NDA. Other subject-specific data such as, Quality of Life questionnaires, independent review of imaging data, etc. are processed and provided to BI by

external vendors and are not part of the EDC. BI plans to provide these data in the CDISC SDTM datasets.

Does the Agency agree?

FDA Response:

Yes, the proposed strategy appears acceptable.

BI Response:

BI acknowledges the FDA's response.

Meeting Discussion:

None

Datasets

QUESTION 7:

BI plans to provide Case Report Tabulation datasets (CDISC SDTM) for the pivotal 1200.32 trial and the supportive trials 1200.22 and 1200.23. SDTM datasets will not be produced for the interim report of the 1200.42 trial.

Does the Agency agree with omitting SDTM for the interim report of trial 1200.42?

FDA Response:

No, datasets should be provided for trials 1200.32, 1200.22, 1200.23, and 1200.42. In addition, an integrated adverse event dataset should be provided for all patients with cancer on BI-conducted trials who have received afatinib. However, blinded data on serious adverse events which have occurred on 1200.131 should be submitted separately.

BI Response:

BI agrees to provide in the NDA submission the following:

- *CDISC SDTM datasets from trials 1200.32, 1200.22, 1200.23, and 1200.42 (Part A only).*
- *An integrated adverse event dataset for all patients with cancer on BI-conducted trials who received afatinib*
- *Provide separately, blinded 1200.131 serious adverse event data*

Meeting Discussion:

None

QUESTION 8:

Reference is made to BI's February 19, 2010 (Serial Number 0554) proposal to provide SAS analysis datasets using a format and variable names that, although similar to ADAM, are specific to BI and would not be those specified for CDISC ADAM formats. BI also proposed to provide SAS programs that could be used with these datasets to reproduce the primary efficacy analyses. See Section 15 for additional details.

Reference is also made to the Agency's response below received on June 11, 2010:

> *The datasets do not need to conform strictly to ADAM structure. The proposed content and structure appears acceptable. However, whether more data will be needed is a review issue. Please also note the following general recommendations.*
>
> - *The formats for the variables that represent the same physical variable across multiple datasets (including multiple tabulation and analysis datasets) should be consistent.*
>
> - *Be careful with the date variables. If they are formatted as SAS date variables, please use the same date format for all date variables so that the numerical operations involving multiple date variables can be done. For example variables representing randomization date and some event date should have the same SAS date informat which will allow one to calculate the time to event just by using arithmetic operations. Please also document in the data definition file what SAS informat is being used for each date variable.*

Additionally, reference is made to the September 24, 2011 Pre-NDA Meeting Granted FAX in which the FDA referenced Data Standards for Studies.

BI has studied the guidance documents for datasets, including "CDER Common Data Standards Issues Document (Version 1.0/May 2011)', and is working towards adopting the guidance. However, during this period of transition the analysis datasets will not be derived directly from the SDTM.

If direct traceability is needed from the analysis datasets to their source, the panel of non-SDTM source datasets could be supplied in SAS XPORT format.

In addition, the battery of programs and macros that build the analysis datasets from their sources could be provided. However, it is anticipated that the complexity of the programs and macros would make it difficult, in some cases, to attempt to trace the data through the collapsing process to its final format in the analysis datasets. Accordingly, BI proposes to send the analysis datsets, but not the source datasets and derivation programs.

Based on the above, please confirm the following:

1. The analysis datasets and associated primary efficacy table programs will be sufficient as initially proposed in February 2010.
2. The source data (which differ in format from the SDTM datasets) and the programs to create the analysis data sets will not be needed for the NDA submission.

FDA Response:

The source data and the macros and programs used to derive the analysis datasets should be provided with the NDA submission.

BI Response:

BI agrees to include the source data and the macros and programs used to derive the analysis datasets in the NDA submission. For adverse events and laboratory tests, BI system dependent macros are used that would not be expected to function as stand alone programs.

Meeting Discussion:

None

4-Month Safety Update Report

QUESTION 9:

BI plans to use a cut-off date near the date of the NDA submission. All available safety information from patients enrolled in the studies included in the NDA and any new studies initiated prior to the cut-off date will be included in the 4-month Safety Update Report.
The 4-month Safety Update Report will utilize the nomenclature for pooling trials (i.e., SAFs) as described in Table 4.1: 1 in APPENDIX 2. BI proposes to update the following ISS analyses:

- Among all patients treated with afatinib, excluding named patient use, investigator initiated studies, healthy volunteers, and patients from the double-blind trial 1200.131 (including SAF-1 through SAF-5).
    - Tabulate the frequency and intensity of the following:
        - AE, SAE, fatal AE, AE leading to dosage reduction of afatinib, and AE leading to discontinuation of afatinib
        - AE classified as renal insufficiency, hepatic impairment, heart failure, interstitial lung disease and other infrequent, but potentially medically significant AE
- Among patients from the pivotal 1200.32 trial (SAF-1)
    - Tabulate transitions of laboratory tests in CTCAE grades from baseline to worst value reported during treatment.

The data in the 4-month Safety Update Report will be presented cumulatively. New safety information will be added to the data previously provided in the original submission.

Does the Agency have any comment about the proposed timing or safety data to be included in the 4-month Safety Update Report?

FDA Response:

You should submit narratives for any deaths on treatment that have occurred and are included in the 4-month Safety Update Report that were not included in the original submission. Please see response to Question 5.

BI Response:

Please clarify if the patient narratives defined in FDA's Response to Question 4 are also required for inclusion in the 4-month Safety Update Report in addition to the death narratives identified above. See response to BI's Question 4 regarding revised proposal (i.e, deaths and AEs leading to discontinuation).

BI agrees to provide the CRFs requested in FDA's response to Question 5.

Meeting Discussion:

The same narrative criteria (see Meeting Discussion for question 4) should be applied to the safety update.

Expanded Access Program (EAP)

QUESTION 10:

Pending positive data from Study 1200.32 and the supportive data from trials 1200.22, 1200.23 and 1200.42 (data to be summarized in the meeting package), BI is planning to offer expanded access to afatinib in the patient population covered by the proposed indication. The rationale for the EAP is based on the fact that there is no targeted therapy specifically approved for NSCLC patients with EGFR mutations (e.g. first-line).

BI is in the process of having a feasibility analysis conducted to assess the number of patients that will enroll into the expanded access trial. In the absence of this information and without knowledge of the final data for the 1200.32 study, we are currently estimating 1500 patients globally will enroll into the trial over the course of eight months. It is planned that upon approval of afatinib and its commercial availability the enrollment into the trial will end and entered patients will be transitioned onto commercial drug.

Based on the August 13, 2009 *Federal Register* notice regarding Expanded Access to Investigational Drugs for Treatment Use, it is our understanding if the requirements outlined in 21 CFR 312.305 are met then (1) it would be acceptable to conduct the protocol under the

existing 67,969 IND and (2) the expanded access use may begin 30 days after FDA receives the protocol or upon earlier notification that the use may begin. Does the Agency agree?

FDA Response:

This will be a review issue pending the results of your pivotal study. Depending on the results of your pivotal trial, if you propose a treatment protocol, you may submit the treatment protocol to your existing IND. Once the Agency receives the treatment protocol, and unless there is a clinical hold issue, you may begin the treatment protocol 30 days after FDA receives the protocol or upon earlier notification by FDA that you may begin.

You will also need to submit a treatment IDE for your test kit.

BI Response:

The planned protocol will enroll patients covered by the proposed indication. Patients will be eligible for enrollment if they have documented EGFR mutation positive NSCLC regardless of methodology (e.g. gene sequencing, PCR test, etc.). Newly diagnosed patients would be required to have an EGFR mutation positive result per the institution's testing methodology, prior to receiving afatinib.

Meeting Discussion:

CDRH recommendation to CDER is that for the EAP patients will be qualified to enter based upon a positive result from the to be submitted PMA test. FDA understands the sponsor's concern that sufficient materials may not be available for testing and will consider this further when data are available.

Additional Comments:

1. **In the future, please request pre-NDA meetings only after data is available from the pivotal trial.**

   BI Response:

   BI would appreciate further clarification at the meeting.

   Meeting Discussion:

   FDA emphasized that they may be able to provide better input to the sponsor if the results of the pivotal trial are available. One possibility would be to submit written questions concerning the technical aspects of the NDA.

2. **You plan to submit CTRs with the following data cutoffs.**

   1200.22: April 2011

1200.23: July 2010

These data cutoffs are > 1 year prior to the proposed NDA submission. Please explain.

BI Response:

The initial data cutoff of February 25, 2010 for Study 1200.22 was determined by the timing of the pre-specified primary analysis (i.e. response rate) in the protocol. BI performed a planned updated analysis based on approximately 75% of PFS events as of April 6, 2011 that will be included as an Interim Clinical Trial Report in the NDA submission.

The data cutoff of July 8, 2010 for Study 1200.23 was determined by the timing of the primary analysis (i.e. OS). BI is planning to include an updated OS analysis for study 1200.23 in the NDA submission. This updated OS analysis is planned for February 2012.

Note: The overall safety cutoff date for the NDA submission (which will include trials 1200.22 and 1200.23) is planned for February 8, 2012.

Meeting Discussion:

The sponsor's plan is acceptable.

Please state the data cutoffs for the adverse events submitted in the safety update.

BI Response:

The planned data cutoff date for the 4-month Safety Update Report is September 7, 2012.

Meeting Discussion:

None

3. **Section 4.1.2 states, "…for trial 1200.41, only the cohort of patients with progressive disease after treatment with a reversible EGFR TKI following diagnosis of an EGFR mutation is included." Please include all data from trial 1200.41.**

BI Response:

BI wishes to clarify that all data from Study 1200.41 will be included in SAF-5 whereas SAF-4 will include only those patients from Study 1200.41 who received previous treatment with a reversible EGFR TKI.

Meeting Discussion:

The sponsor will provide data for all 3 cohorts.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

None

Minutes Preparer:

{See appended electronic signature page}

Amy Tilley
Regulatory Project Manager

Meeting Chair:

{See appended electronic signature page}

Virginia Maher, M.D.
Clinical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY R TILLEY
12/12/2011

VIRGINIA E MAHER
12/12/2011

FAX

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Pages, including cover sheet: 22		**Date:**	**February 2, 2010**

RE: Preliminary minutes for IND 67,969

Dear Ms. Christoforides:

The attached consists of meeting minutes obtained at the meeting that occurred December 15, 2009, between you and the Division of Drug Oncology Products. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the meeting. If any modifications to these minutes or additional questions for which you would like FDA feedback arise, please contact the Regulatory Project Manager.

Thank you

LCDR Allison Adams-McLean
USPHS
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Drug Oncology Products

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 15, 2009
TIME: 3-4: PM
LOCATION: CDER WO 22 Room 1419
APPLICATION: IND 67969
DRUG NAME: BIBW 2992
TYPE OF MEETING: Pre NDA/Type B

MEETING CHAIR: V. Ellen Maher, M.D.

MEETING RECORDER: Allison Adams-Mclean

FDA ATTENDEES: (Title and Office/Division)

Robert Justice, M.D., M.S., Division Director
Constance Robinson-Kuipieri, Regulatory Information Specialist
Haleh Saber, Ph.D., Supervisory Pharmacologist
Elmika Pfuma, Ph.D., Clinical Pharmacology Reviewer
Jeannie Fourie, Ph.D., Clinical Pharmacology Reviewer Acting Team Leader
Maria Chan, Director Division of Immunology & Hematology Devices
Donna Roscoe, CDRH OVID Reviewer
Shakun Malik, M.D., Medical Officer
Anthony J. Murgo, M.S., FACP, Associate Director OODP IO, Acting Deputy Director
Zei Pao Huang ,Edata Support Team Leader
Tang Shenghui, Ph.D, Statistics Acting Team Leader
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V. Ellen Maher, M.D., Clinical Team Leader
Allison Adams-McLean, RN, BSN, MHA, Senior Regulatory Project Manager
Alice Kacuba, RN, MSN, RAC, Chief, Project Management Staff

EXTERNAL CONSTITUENT ATTENDEES:

Dan Cotton, Senior Associate Director Biostatistics
Dieter Janku, Project Data Manager
James Love, Project Statistician
Pam Strode, DRA Group Lead
Robin Christoforides, Senior Associate Director, DRA
Melidi Shahidi, Global Clinical Development Lead
Rainer Kleemann, International Project Leader
Peter Stopfer, Project Clinical Pharmcokineticist

Martin Stefanic, Clinical Research Oncology, Germany
Bernard Boehm, R&D Project Leader
Edwin Dewit, Therapeutic Area Director
Thomas Schindler, Head Medical Writing Europe
Ingrid Schultz, International Team Member DRA
Ellen Gold, Drug Safety Physician
Huiping Jiang, Drug Regulatory Affairs

BACKGROUND:

This pre-NDA meeting was held to discuss a study in which BIBW 2992 is administered to patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one reversible epidermal growth factor receptor (EGFR) inhibitor. The sponsor submitted a pre-NDA Type B Meeting Request on September 16, 2009and subsequent background package to facilitate the meeting.

DISCUSSION POINTS:

Question 9.1:

As noted in Section 6, in accordance with the FDA Guidance for Industry entitled, "Fast Track Drug Development Programs – Designation, Development, and Application Review," BI proposes to submit the NDA as a Rolling Review in two Reviewable Units in ICH eCTD format as follows:

Reviewable Unit Number	Brief Description	Targeted Timelines
Reviewable Unit # 1	Nonclinical Data (without Nonclinical Overview)	May 2010
Reviewable Unit # 2	Clinical and Quality (with Nonclinical Overview)	September 2010*

* Since 1200.23 is an event driven trial the targeted timelines for submission of Reviewable Unit # 2 may change

The first Reviewable Unit will contain the pertinent documentation in Modules 1, 2 and 4 to provide a complete nonclinical pharmacology and toxicology package for review (see Comprehensive Table of Contents for Reviewable Unit # 1 in APPENDIX 1). Per the FDA's requirement, the User Fee will be paid at the time of the Reviewable Unit # 1 submission.

As noted in the FDA Guidelines entitled, "M4S: The CTD-Safety," the "Nonclinical Overview" (Module 2, Section 2.4) is interdependent on the clinical and biopharmaceutical data. BI proposes to include the "Nonclinical Overview" in the

submission of the Reviewable Unit # 2 (i.e., complete submission) to allow for the integration of the clinical data.

Reviewable Unit # 2 (Clinical and Quality) will contain the remaining documentation in Modules 1, 2, 3 and 5, including the "Nonclinical Overview" that will serve as the complete NDA submission (see Comprehensive Table of Content for Reviewable Unit # 2 in APPENDIX 1).

The following questions pertain to BI's proposal to submit a rolling NDA:

a) Does the Agency agree with BI's proposal to submit a rolling NDA according to the targeted timelines noted above?

FDA Response: Yes.

b) If yes, does the Agency agree that it is acceptable to submit the "Nonclinical Overview" with Reviewable Unit # 2?

FDA Response: No. Your entire pharmacology toxicology data should be submitted with Unit 1.

BI Response: BI agrees to submit a Nonclinical Overview with Reviewable Unit 1 (May 2010). In addition, BI plans to submit a revised Nonclinical Overview with Reviewable Unit 2 (September 2010) that will integrate the clinical data that will not be available at the time of the Reviewable Unit 1 (May 2010) submission.

Does the Agency agree?

Meeting Discussion: Yes, the sponsor will identify the new information in the revised version.

Question 9.2:

BI will electronically submit the NDA in ICH Common Technical Document (CTD) format. Does the Agency have any comments about the general organization or content of the information provided in Reviewable Unit # 1 or Reviewable Unit # 2 as outlined in the Comprehensive Table of Contents (see APPENDIX 1)?

FDA Response: See response to question 9.1.

Question 9.3:

Does the Agency have any comments on the organization and/or information proposed to be included in Module 2.7.1 entitled, "Summary of Biopharmaceutics and Associated Analytical Methods (see APPENDIX 2)?"

FDA Response: Your summary appears acceptable from a Clinical Pharmacology Perspective.

Question 9.4:

The following questions pertain to Module 2.7.2 entitled, "Summary of Clinical Pharmacology Studies":

a) Does the Agency agree with the proposed classifications to be used for the hepatic impairment population pharmacokinetic (PK) analysis? These classifications are based on the following modified specification of the National Cancer Institute (NCI) Organ Dysfunction Working Group (see Section 11.3.1):

Liver Dysfunction group	Transaminase Levels	Total Bilirubin Levels
Control	AST and ALT≤ULN	BIL≤ULN
Mild 1	AST and ALT≤2.5xULN	BIL≤ULN
Mild 2	AST or ALT≤10xULN	BIL≤1.5xULN
Moderate	AST and ALT≤10xULN	1.5xULN<BIL≤3xULN

FDA Response: The proposed classification of hepatic impairment based on NCI-ODWG appears acceptable from a Clinical Pharmacology perspective. The adequacy of the data to support labeling will be a review issue.

Population PK approach using phase 2 and 3 data can be useful to assess the impact of hepatic impairment on the PK of your drug. To be useful, these analyses usually include patients with a wide range of hepatic function from phase 2/3 studies with enough PK samples from each patient to characterize their PK. Typically the analysis is pre-planned to get precise estimates (relative standard error ≤ 20%) of the mean clearance parameter in hepatic impaired patients. For further information, see the population PK guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf

Depending on the size of the effect on clearance, you may also need to study patients with severe hepatic impairment in order to develop specific dosing recommendations in this patient population. Please refer to the guidance for industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function" at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf

b) As discussed in Section 11.3.2, BI is planning to conduct Study 1200.86, a dedicated hepatic impairment trial in non-cancer patients with liver cirrhosis in accordance with the Guidance for Industry entitled, "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling". The data will not be available at the time of the NDA submission. BI proposes to provide the results of this trial post-approval. Does the Agency agree?

FDA Response: Yes. Please submit your final protocol for study 1200.86 for review.

c) Does the Agency agree with the proposed PK-Efficacy and PK-AE correlations described in Section 11.3.3?

FDA Response: Your plan appears acceptable from a Clinical Pharmacology perspective. Please refer to the guidance for industry entitled "Exposure Response Relationships" at
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072109.pdf

d) As discussed in Section 11.3.4, BI is conducting Study 1200.24, a dedicated QT study in patients with relapsed or refractory solid tumors. BI anticipates that the study may not be completed at the time of the NDA submission. In this situation, BI proposes to provide the results of this trial post-approval. Does the Agency agree?

FDA Response: Your proposal appears acceptable from a Clinical Pharmacology perspective.

e) Does the Agency have any comments on the organization and/or information proposed to be included in Module 2.7.2 entitled, "Summary of Clinical Pharmacology Studies" (see APPENDIX 3)?

FDA Response: Your proposal appears acceptable from a Clinical Pharmacology perspective.

Question 9.5:

The following questions pertain to Module 2.7.3 entitled, “Summary of Clinical Efficacy” (SCE):

a) Does the Agency agree that the planned tables and figures for the analysis of survival are adequate as described in Section 3.2.1.1 of the mock SCE (see APPENDIX 4)?

FDA Response: Yes.

b) Does the Agency agree that the proposed tables and figures for the analysis of progression-free survival (PFS), together with the censoring rules and associated sensitivity analyses are adequate as described in Sections 1.3.4 and 3.2.1.2.1 of the mock SCE (see APPENDIX 4)?

FDA Response: It appears reasonable.

c) If there are any additional analyses to support the NDA submission that are not included in the respective clinical trial report(s), BI proposes to place the supportive tables, figures and listings that may be referenced in the SCE (Module 2.7.3) as a separate document in Module 5.3.5.3 Does the Agency agree?

FDA Response: Yes. Please provide links between these two modules.

d) Does the Agency have any comments on the organization and/or information proposed to be included in Module 2.7.3 entitled, “Summary of Clinical Efficacy” (see APPENDIX 4)?

FDA Response: No.

Question 9.6:

The following questions pertain to Module 2.7.4 entitled, “Summary of Clinical Safety” (SCS):

a) Does the Agency agree with the grouping of studies for the proposed combined safety analysis as summarized in Table 11.2.1: 1 and as described in Sections 1.1.1 – 1.1.3 of the mock SCS (see APPENDIX 5)?

FDA Response: Study 1200.22 included patients with NSCLC treated with 40 or 50 mg of study drug. You plan to include these patients in SAF-2 (all patients treated at 50 mg) and SAF-4 (all patients treated at 40 mg). Further, you will provide a study report for 1200.22. It is not necessary to include SAF-3 (study 1200.22) as a separate grouping in your SCS.

BI Response: BI agrees not to include SAF-3 as a separate grouping in the SCS and will re-number the SAF groupings accordingly.

b) Does the Agency have any comments regarding the proposed content and format of the Integrated Summary of Safety (ISS) as described in Section 11.2.1? The analyses will include all BIBW 2992-treated patients who had started treatment no later than six weeks prior to the cut-off date (i.e., Study 1200.23 database lock date).

FDA Response: Yes. See 9.6.a, 9.6.d, and 9.14.

c) Does the Agency agree that supportive tables, figures and listings referred to in the SCS (Module 2.7.4) as a separate document are best placed in Module 5.3.5.3?

FDA Response: Yes.

d) Does the Agency have any comments on the organization and/or information proposed to be included in Module 2.7.4 entitled, "Summary of Clinical Safety" (see APPENDIX 5)?

FDA Response: In Table 11.2.1, you state the analyses that will be provided in the SCS for various patient groupings (SAF-1 to SAF-7). Please include an analysis of:

a. Adverse events in all patients;
b. Pre-defined adverse events of special interest in all patients;
c. Safety in special populations in all patients; and
d. Rare but potentially clinically relevant AEs in patients treated with 50 mg of study drug.

BI Response: BI will provide the requested analyses, as indicated by the bolded/capitalized revisions to Table 11.2.1: 1 shown below

Does the Agency agree with the revised analyses?

Meeting Discussion: The sponsor will submit SAF-3 as planned originally.

REVISED Table 11.2.1: 1 ISS safety analyses conducted for the different safety analysis sets and study groupings

SAF set	Standard analysis of AEs	AEs leading to dose reduction or discontinuation	Pre-defined AEs of special interest	Laboratory safety parameters	Safety in special populations	Rare but potentially clinically relevant AEs
SAF-1 (pivotal 1200.23 trial)	Yes	Yes	Yes	Yes	Yes[1]	**YES**
SAF-2 (50 mg starting dose)	Yes	Yes	Yes	Yes	Yes	**YES**
SAF-3 (open-label trial 1200.22)	**DELETED**					
SAF-4 (40 mg starting dose)	Yes	Yes	Yes	Yes	No	**YES**
SAF-5 (various study groupings)	Yes	No	No	No	No	**YES**
SAF-6 (all patients)	**YES**	**YES**	**YES**	No	**YES**	Yes
SAF-7 (healthy volunteers)	Yes	No	No	No	No	No

[1]In the clinical trial report, not in the SCS.

e) As discussed in Section 11.2.2, BI plans on grouping MedDRA preferred terms in order to optimize the assessment of selected EGFR-related adverse events. Does the Agency agree with BI's proposal?

FDA Response: Yes. Please footnote all tables so we can easily determine which preferred terms were grouped to obtain the incidence of each adverse event presented in a table.

BI Response: BI will annotate the tables to indicate which entries are grouped terms, with a footnote referring to a table that lists the constituent MedDRA preferred terms.

Does the Agency agree with this approach?

Meeting Discussion: Plan appears acceptable.

Question 9.7:

As noted in Section 11.2.1, BI believes that Module 2.7.4 coupled with supportive tables, figures, and listings in Module 5.3.5.3 constitutes an adequate Integrated Summary of Safety (ISS). Does the Agency agree?

FDA Response: Yes.

Question 9.8:

Boehringer Ingelheim intends to submit one executed batch record (EBR) for each of the three strengths (30 mg, 40 mg [redacted] (b) (4) intended for market. The EBR will be selected from the pivotal Phase 3 batches and/or the primary stability batches manufactured at the commercial manufacturing site in Ingelheim, Germany. The selected EBRs will be fully representative of the commercial manufacturing process.

Does the Agency agree with the number and the selection of the executed batch records for submission?

FDA Response: The proposal to submit one executed batch record each of the three strengths is acceptable. However, also include one unexecuted batch record for each of the three strengths representing the proposed commercial process.

Question 9.9:

Boehringer Ingelheim proposes to structure the Methods Validation Package (Section 3.2.R.2) according to the FDA draft Guidance for Industry Analytical Procedures and Methods Validation, August 2000. The drug product and drug substance documentation, e.g., analytical procedures and validation reports, specifications, etc, in the Methods Validation Package will be provided via hyperlink to the corresponding documents located in the other sections of Module 3 of the eCTD NDA.

Does the Agency agree with the strategy for formatting the methods validation section?

FDA Response: Yes.

Question 9.10:

The chemistry, manufacturing, and controls information will be organized in the ICH Common Technical Document (CTD) format in Module 3: Quality. Module 3 will be comprised of one section for BIBW 2992 MA2 drug substance (3.2.S) and one drug product section (3.2.P) for BIBW 2992 MA2 Film-Coated tablets that will include four (4) tablet strengths. Throughout Module 3, sections where no information is filed will be omitted from the NDA submission per ICH Guidance for Industry M4: The CTD – General Questions and Answers, December 2004. Tentatively, the sections BI will not include are: 3.2.S.2.5 Process Validation and/or Evaluation, 3.2.P.3.5 Process Validation and/or Evaluation, and 3.2.P.4.6 Novel Excipients. Additional sections for which no information is filed may be added to this list.

The Pharmaceutical Development (3.2.P.2) section will be presented as a single document summarizing the development work for all four dosage strengths.

One Control of Excipients section (3.2.P.4) will be presented for all compendial (USP/NF) excipients. A separate Control of Excipients section will be presented for the non-compendial excipient FD&C Blue #2 (b) (4).

The overall organization and proposed content of Module 3 is presented in APPENDIX 11.

Does the Agency have any comments about the organization and/or proposed content to be included in Module 3?

FDA Response: In general your proposal is acceptable. It is preferred that a notation is made under the heading for each section left blank, that the section is not applicable.

BI Response: BI will identify those sections that are not applicable in the Quality Overall Summary (QoS). In accordance with Appendix 3 of the eCTD Specification, the not applicable sections will be omitted from the application.

Question 9.11:
Does the Agency have any comments about the general organization and/or proposed content to be included in Module 4 (see APPENDIX 1)?

FDA Response: In Module 4, an STF should be used for each cross referenced document; use the pre-clinical legacy study report tag. Each study ID should include -1, -2, -3, or –a,

-b, -c at the end since using the same study ID as the original STF could pose an issue.

BI Response: BI will create STFs within Module 4 as recommended.

Question 9.12:

Does the Agency have any comments about the general organization and/or proposed content to be included in Module 5 (see APPENDIX 1)?

FDA Response: For ease of review, navigation and efficiency, the narratives should be provided as a single bookmarked PDF, with a linked table of contents which categorizes the narratives by deaths, discontinuations, withdrawals, and other serious adverse events.

BI Response: Please clarify if the request is to combine all patient narratives for all trials in one PDF? If yes, based on the number of anticipated narratives to be provided the file may be larger than 100 MB in size and would therefore need to be split in accordance with eCTD specification requirements. As such, BI proposes to provide single bookmarked PDF per trial.

Does the Agency agree?

Meeting Discussion: This is acceptable providing there is a table of contents with adequate bookmarks and navigating ability. The narratives should be sub-categorized as described above.

Please see response to Question 9.14.

As noted in Question 9.14, BI defines "withdrawals" as follows:

All adverse events that led to permanent discontinuation of BIBW 2992. Events that only led to a dose reduction or additional concomitant therapy (other than those reported as serious adverse events) will not be included as dose reduction and supportive care based on the clearly defined scheme constitute the dosing regimen in all trials of BIBW 2992

Does this reflect the Agency's expectation for withdrawals?

Meeting Discussion: The FDA agrees that study withdrawal is permanent discontinuation of study drug due to an adverse event.

Please provide the SAS programs in the submission.

BI Response: For efficacy analyses, BI will provide SAS programs for the pivotal trial 1200.23 that can be used with the accompanying datasets to reproduce the analyses of Overall Survival and PFS.

BI could provide programs that were used to produce the SCS analyses listed in the revised Table 11.2.1:1 (see BI Response to Question 9.6 (d)). However, almost all of the SCS programs depend upon an extensive library of macros constructed by BI. The SCS programs cannot reproduce the SCS analyses without the macros.

Therefore, BI proposes not to send the SCS programs. Instead, BI will provide datasets and documentation that support the SCS, as described for Question 9.16.

Meeting Discussion: The proposal for submitting SAS programs for efficacy is acceptable. The sponsor will provide a source dataset and an analysis dataset for the tables in SCS. The sponsor will also submit a document cross referencing specific tables with datasets and programs. The FDA will review this as time permits.

Please provide the data definition files in .pdf format.

BI Response: For analysis datasets, BI will provide the data definition files in .pdf format. For the tabulation datasets in CDISC SDTM format, BI was planning to provide them in .xml format in accordance with the instructions provided in the Study Data Specifications (Version 1.5).

Does the Agency agree?

Meeting Discussion: See above. Indicate version of Medra to be used.

Question 9.13:

The original NDA submission will contain two trials that were conducted in patients with NSCLC. Study 1200.23, a Phase IIb/III study, will provide the pivotal data to establish the efficacy of BIBW 2992 for the proposed indication (see Section 3). Study 1200.22, a Phase II study, will provide supportive data on longer-term effectiveness and safety.

In accordance with Guidance for Industry entitled, "Integrated Summary of Effectiveness (ISE) [April 2009], BI has addressed all of the context requirements of an ISE in Section 2.7.4 (Summary of Clinical Efficacy – see APPENDIX 4). Since Study 1200.23 is the only pivotal trial in this submission, all analyses that are required for an ISE will be performed as part of the Clinical Trial Report and will be included in the statistical appendix. Therefore, BI does not believe that it is necessary to provide a specific ISE in Module 5.3.5.3. The differences in the design of the 1200.23 pivotal and 1200.22 supportive studies (e.g., patient population, randomized placebo-controlled vs. non-randomized) preclude a pooling of the efficacy data from the two trials.

The trial reports will present all source data as appendices, including detailed results from statistical analysis software and listings of derived data used in the analyses. If additional analyses become necessary after unblinding, these will be placed in a separate report in Module 5.3.5.3.

Based on the above, BI does not believe that it is necessary to provide a specific ISE in Module 5.3.5.3. Does the Agency agree?

FDA Response: This is acceptable if the Summary in 2.7.4 provides an adequate analysis of efficacy data.

Question 9.14:

In accordance with the Guidance for Industry entitled, "Structure and Content of Clinical Study Reports," BI is planning to provide patient narratives for the following events, with the exceptions noted:

a) All deaths of BIBW 2992-treated patients that occurred during the study (including the post-treatment follow-up period of 28 days), and those deaths reported after the 28 day follow-up period that were considered related to study drug, with the exception of those deaths due to progression of underlying disease. Please note, the defined post-treatment follow-up period was not consistently defined across protocols. For the purpose of the NDA submission, BI will use the period of 28 days as noted above, regardless of the "follow-up period" defined in the individual trials.

b) All other serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths).

c) All adverse events that led to permanent discontinuation of BIBW 2992. Events that only led to a dose reduction or additional concomitant therapy (other than those reported as serious adverse events) will not be included as dose reduction and supportive care based on the clearly defined scheme constitute the dosing regimen in all trials of BIBW 2992.

d) All patients with ILD (interstitial lung disease)-like events who will be selected after a thorough medical review of all cases identified by a Standardized MedDRA Query (SMQ) search.

e) All patients with a decrease in left ventricular ejection fraction (LVEF) which is more than 20% from baseline and below the institution's lower limit of normal. If the institution's lower limit of normal is not known, a lower limit of normal value of 50% will be used.

f) All patients with cardiac failure events who will be selected after a thorough medical review of all cases identified by a Standardized MedDRA Query (SMQ) search.

BI believes that in order to provide an accurate medical review for the NDA, narratives should be provided for those patients who participated in any trial for which a Clinical Trial Report (i.e., completed study) or Interim Report (i.e., ongoing study) has been provided in the original NDA submission and meet the criteria noted above. BI does not plan to provide patient narratives for any newly initiated or ongoing trials (with the exception of those with an Interim Report) for the original NDA submission or the Safety Update Report. Narratives will therefore be provided for all patients from the pivotal (1200.23) and supportive (1200.22) trials who have been treated with BIBW 2992 and meet the criteria noted above. Overall, narratives will be provided in the NDA submission for approximately 75% of all patients who have been treated with BIBW 2992 at a starting dose of 50 mg, and approximately 70% of

NSCLC patients ever treated with BIBW 2992 at any starting dose. We believe that this will accurately reflect the profile of the patient population for the proposed indication.

For those trials for which a report has been submitted, additional narratives will not be provided for those patients that may be continuing on therapy after the date of the report. This includes Trials 1200.22, 1200.23 and all ongoing studies.

The narratives will take into account all available information on the respective patient, will be medically reviewed, and will include a medical assessment. The event terms will be coded using MedDRA Version 12.1.

The placement of the narratives is outlined in the electronic submission proposal (see Section 3 of APPENDIX 9). A copy of the narrative template is provided in APPENDIX 10.

The following questions pertain to the proposed patient narratives BI intends to provide in the original NDA submission:

a) Does the Agency agree with the selected events in which a patient narrative will be provided for in the original NDA submission?

FDA Response: In b above you state, "serious adverse events (other than death, but including the serious adverse events temporally associated with or preceding the deaths)" will be included as a separate narrative. It is not necessary to write two narratives. Please include all temporally related events in the patient's death narrative.

b) Does the Agency agree with the criteria chosen to identify those studies in which patient narratives will be included in the original NDA submission?

FDA Response: Yes.

c) Based on the above, BI believes that it is not necessary for the review of the NDA to include patient narratives in the Safety Update Report. Does the Agency agree?

FDA Response: No. Narratives should be provided for subjects with updated safety data or new SAEs.

BI Response: For those trials for which patient narratives have been provided in the original NDA (i.e. Reviewable Unit 2), BI will provide an updated and/or new narrative based on new safety data and/or new SAEs, if applicable.

Question 9.15:

In accordance with 21 CFR 314.50(f)(2), BI is planning to provide CRFs in the original NDA submission for the pivotal Phase III Study 1200.23 and the supportive Phase II Study 1200.22 for each patient who died or who did not complete the study because of an adverse event, whether believed to be drug-related or not, including patients receiving BIBW 2992 or placebo. For all other studies that will be included in the NDA and Safety Update Report, BI does not plan to provide CRFs for the review of the NDA as the majority of patients in

these studies represent different patient populations. The CRFs that will be provided for Studies 1200.23 (pivotal) and 1200.22 (supportive) will adequately represent the patient population for the proposed indication.

Does the Agency agree?

FDA Response: Please also provide CRFs for all patients with a serious adverse event in Study 1200.23 (key study) and Study 1200.22 (supportive study).

BI Response: BI agrees to provide CRFs for all patients with a serious adverse event (SAE) while on treatment as well as all drug-related SAEs 28 days post-treatment for trials 1200.23 and 1200.22.

Question 9.16:

For Studies 1200.22 and 1200.23 electronic data capture was used and all information from the eCRFs will be submitted to the NDA as Case Report Tabulations (CRTs) in CDISC format. As described in Section 4.1 of the electronic submission proposal (see APPENDIX 9), BI does not plan to provide additional CRTs for all other ongoing/completed trials that will be included in the NDA.

Does the Agency agree?

FDA Response: Please clearly and briefly state the datasets you will submit to support the SCS.

BI Response: As a point of clarification regarding the Case Report Tabulations, does the Agency agree with BI's proposal in Question 9.16 to provide CDISC SDTM compliant datasets for trials 1200.22 and 1200.23 only and not for any other trial?

Regarding the datasets used for analysis, BI will provide SAS XPORT (.xpt) format datasets that were used to support the SCS analyses for SAF-1, SAF-2, SAF-4, and SAF-6 described above in the revised Table 11.2.1:1 (see BI Response to Question 9.6 (d)). The structure of these datasets will be compliant with the Data Standard (UCM189445.pdf). However, these datasets will use a format and variable names that are specific to BI and will not be those specified by CDISC ADAM format

Meeting Discussion: See above.

Question 9.17:

BI will provide SAS export datasets for the 1200.22 and 1200.23 efficacy analyses that will form the basis of the SCE. According to Section 4.1 of the electronic submission proposal (see APPENDIX 9), BI does not plan to provide any additional datasets for efficacy and/or safety. Does the Agency agree?

FDA Response: It appears reasonable. However please clarify which datasets you will be providing SAS export datasets or SAS transport datasets. Please refer to the following web site to prepare the datasets: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM189445.pdf

BI Response: BI will provide SAS datasets in XPORT format for the 1200.22 and 1200.23 efficacy analyses. The structure of these datasets will be compliant with the Data Standard document (UCM189445.pdf). However, these datasets will use a format and variable names that are specific to BI and will not be those specified for CDISC ADAM format.

In keeping with the following provision on page 5 of the referenced Data Standard document, BI would like to do everything practical to make sure that the datasets delivered with the NDA will meet the reviewer's needs:

> "*Prior to submission, sponsors should contact the appropriate center's reviewing division to determine the division's analysis dataset needs"*

Please advise if there are specific reviewers or disciplines (e.g. Biostatistics) within the Division to whom BI can provide details of the proposed format and content of datasets, and from whom BI can receive feedback.

Question 9.18:

Does the Agency have any comments related to the electronic submission proposal or the proposed structure and/or format of the tabulation and analysis datasets (see APPENDIX 9)?

FDA Response: See response to Question 9.16.

Question 9.19:

Does the Division agree with the "indication" metadata that provides the structure for Module 5.3.5.3 (see APPENDIX 1)?

FDA Response: Yes.

Question 9.20:

BI does not plan to include pharmacokinetic raw data files in the NDA. These data are available upon request. Does the Agency agree that these data are not necessary for the review of the planned NDA?

FDA Response: No, all data sets to calculate PK parameters should be submitted as SAS transport files (*xpt). All data sets used for model development and validation in your population PK analyses should be submitted as SAS transport files (*xpt). A description of each data item should be provided in a Define.pdf file. Any concentration or subject

that has been excluded from your analyses should be flagged and maintained in the data set.

BI Response: BI proposes to submit the datasets for the following trials (for noncompartmental analysis):

- 1200.1, 1200.2, 1200.3, 1200.4: Basic PK characteristics in cancer patients
- 1200.25: Human ADME trials in healthy volunteers
- 1200.35: Relative BA trial in healthy volunteers
- 1200.80: Proportional Similarity trial with final formulation
- 1200.79: Drug-drug interaction trial with ritonavir

BI plans to transform PK analysis data sets (BI format) into SAS XPORT files (*.xpt). The BI internal PK analysis data sets have a similar format and content as the PK Data file 4+, 5+ and 6+ as described in the attached document entitled, "Description of Analytical Transfer Files and PK/PD Data Files". The SAS program for the generation of the PK analysis data sets would also be provided.

Does the Agency agree?

Meeting Discussion: This is acceptable.

Attachment: "Description of Analytical Transfer Files and PK/PD Data Files"

Adobe Acrobat Document

BI does not plan to provide PK datafiles for noncompartmental analysis for the following trials:

- 1200.5: Phase II combination of BIBW 29929 with letrozole for the indication of Breast cancer
- 1200.6: Phase I combination of BIBW 2992 with docetaxel
- 1200.20: Phase I combination of BIBW 2992 with docetaxel
- 1239.1: Phase I combination of BIBW 2992 with BIBF 1120)
- 1239.2: Phase II combination of BIBW 2992 with BIBF 1120 in colorectal cancer patients
- 1239.3: Phase II combination of BIBW2992 with BIBF 1120 as well as Phase II monotherapy with BIBW 2992 in hormone refractory cancer patients)

Does the Agency agree?

Meeting Discussion: This is acceptable.

Question 9.21:

As discussed in Section 11.2.3, for the original NDA, BI plans to use the database lock date for Study 1200.23 as the cut-off date for the SCS. For the Safety Update Report (i.e. 2-month presumed for priority review or 4-month for standard review) BI plans to use the submission date as the cut-off date. The proposed content of the Safety Update Report is described in Section 11.2.3. Does the Agency have any comment about the proposed safety dataset to be included in the 2-Month/4-Month Safety Update Report?

FDA Response: You plan to provide safety updates for SAF-2 (all patients treated at 50 mg) and SAF-4 (all patients treated at 40 mg). This will include all AEs, SAEs, and AEs leading to dose reduction or discontinuation. You also plan to provide a safety update of infrequent, but potentially medically significant AEs in SAF-6 (all treated patients).

- **Please include AEs leading to patient deaths in your update of SAF-2 and 4.**
- **Please provide a safety update for all AEs, SAEs, AEs leading to discontinuation, and AEs leading to death in your key study.**
- **Please provide a safety update for all AEs, SAEs, AEs leading to discontinuation, and AEs leading to death in SAF-6.**
- **Please provide updated datasets to accompany this report.**

BI Response: BI will provide the above information in the safety update report.

Question 9.22:

Reference is made to the End-of-Phase 1 third/fourth-line NSCLC teleconference held on July 31, 2007 at which time FDA agreed that BI should submit a pediatric waiver request since there are too few children with NSCLC to study. BI submitted on August 29, 2007 (IND Serial Number 0177) a pediatric waiver for NSCLC. BI plans to resubmit the waiver request in the NDA if a response is not obtained by the time of submission. Does the Agency agree?

FDA Response: FDA will review the pediatric waiver request as part of the NDA package.

Question 9.23:

Pending positive data from Study 1200.23 and considering the unmet medical need, BI is planning to offer expanded access to BIBW 2992 in the patient population covered by the proposed indication. Based on the August 13, 2009 *Federal Register* notice regarding Expanded Access to Investigational Drugs for Treatment Use, it is our understanding if the requirements outlined in 21 CFR 312.305 are met then (1) it would be acceptable to conduct the protocol under the existing 67,969 IND and (2) the expanded access use may begin 30 days after FDA receives the protocol or upon earlier notification that the use may begin. Does the Agency agree?

FDA Response: Yes, you may submit a treatment protocol to your IND to provide for your expanded access.

Additional Comments:

1. **Please provide only a high level overview in future pre-NDA meeting packages.**

2. **Additional information (data or analyses) may be requested during the review.**

3. **Please fill out this table for each of your pivotal studies and include it in Module 1 of your NDA submission. This way we can choose the inspection sites as soon as the application comes in.**

Site **Address** **Point of Contact**	**# Enrolled**	**Median OS**	**# Gr 3-4 AEs**	**# Major Protocol Violations**

BI Response: BI will provide the requested table in the 1200.23 Clinical Trial Report and in Module 1 with the proposed modifications below noted in bold/red text. Does the Agency agree with BI's proposed revisions to the table?

Site	**# Enrolled**	**Median OS** **Placebo[1]**	**Median OS** **BIBW 2992[1]**	**# Gr 3-4 AEs**	**# Major Protocol Violations**
Address					
Point of Contact					

[1]For sites with small numbers of patients the survival times will be provided for each patient.

4. **CDRH comments as follows:**

- **Based on the BI 10 November reply to queries about EGFR testing, it isn't clear whether EGFR mutant-positive patients are over-represented in trial 1200.23, compared to the population in the BI proposed indications for use: "patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one reversible Epidermal Growth Factor Receptor (EGFR) inhibitor." CDRH recommends that BI clarify whether the testing they have described, or other testing known to them, has enriched for mutation positive patients in the trial population compared to the "Indications and Usage" population.**
- **It isn't clear how BI plans for data from a marker positive only trial (1200.22) to "provide supportive data on longer-term effectiveness and**

safety" concerning the mixed population studied in trial 1200.23 and cited in the proposed "Indications and Usage".

The following are Test issues:

- **DxS, the manufacturer of the EGFR mutation test, is now owned by Qiagen and the previous versions 1 and 2 of the DxS test, implemented on the Roche Light Cycler, will not be available for U.S. review and approval. If BI plans eventually to propose drug labeling that reflects performance of BI 1229 in EGFR mutation positive or negative subpopulations, BI should advise CDRH concerning plans for availability of clinical trial specimens/materials needed to validate the final version of the EGFR mutation test. BI should be informed that the expectation is that most if not all the samples from the clinical trial (screen negative and screen positive) will be evaluated with the final test version.**
- **BI should indicate when they plan on having the final test complete, and whether it will be available for use in enrolling patients during a clinical trial.**
- **If the final version of an EGFR mutation test will not be available for use in enrolling patients during a clinical trial, BI should submit a plan for a bridging /concordance study between the version of the test used for enrollment and the final version intended for market. BI was advised previously of the business risks associated with a bridging study (refer to response to 1200.32 Special Protocol Assessment serial number 0369 where the test is discussed).**

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-67969	GI-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	BIBW-2992 MA2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALLISON ADAMS-MCLEAN
02/02/2010

MEETING MINUTES

MEETING DATE: October 16, 2008 **TIME: 10 – 11 am LOCATION: 1309**

IND: 67,969 **Meeting Request Submission Date:** June 25, 2008
FDA Response Date: August 13, 2008
Briefing Document Submission Date: September 10, 2008

DRUG: BIBW 2992

SPONSOR: Boehringer Ingelheim **TYPE of Meeting:** Type B, Phase 3

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(b) (4)

MEETING OBJECTIVES: To discuss the existing clinical data to support the conduct of Study 1200.32 and the overall study design specific to endpoints and statistical analyses.

BACKGROUND: The sponsor's drug, BIBW 2992, is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) (b) (4)

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

LIST OF SPECIFIC QUESTIONS, GROUPED BY DISCIPLINES

CLINICAL - STUDY 1200.32

Adequacy of Supportive Data

8.1 As discussed in Sections 13 and 15.2, BI believes that the preclinical and clinical results obtained to date, and specifically the interim results of Study 1200.22 (i.e., Phase II second-line NSCLC study in patients whose tumors have activating epidermal growth factor receptor [EGFR] mutations), support the conduct of a first-line Phase III trial (Study 1200.32) in NSCLC enriched for the presence of EGFR mutations. Does the Agency agree?

BI Rationale:

- The currently available preclinical data as well as the clinical data from Study 1200.22 suggest that the potency of BIBW 2992 is in the range of reversible EGFR TKIs.
- There is considerable concordance between the characteristics (i.e., histology and smoking history) of the genotypically enriched patient population in Study 1200.22 and the proposed demographically enriched patient population in Study 1200.32.
- Treatment with reversible EGFR tyrosine kinase inhibitors (TKIs) in patients with adenocarcinoma, who have a never-smoking (<100 lifetime cigarettes) or light smoking history (<15 pack years and quit >1 year before), has shown considerable efficacy. Activating EGFR mutations are

seen in 27-60% of these patients.

- An independent Data Monitoring Committee (DMC) will oversee the conduct of the study to ensure safety of all trial participants, which will include a regular assessment of the potential negative effects of the investigational arm.

FDA Response: Possibly. Our response may also be influenced by any results that become available from Study 1200.23.

Patient Population

8.2 As discussed in Sections 13.1, 14.1 and 14.2, BI proposes to demographically enrich the patient population of Study 1200.32 by enrolling patients with NSCLC, adenocarcinoma subtype, who have a history of never smoking or light smoking to support the proposed indication in Section 3. Does the Agency agree that this is an acceptable patient population to support a registration of BIBW 2992 monotherapy for the following proposed indication?

> *BIBW 2992 is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)* (b) (4)

BI Rationale:

- Study 1200.32 is designed to evaluate the efficacy of BIBW 2992 monotherapy treatment based on both demographic and genotypic (presence of activating EGFR mutations) features.
- The incidence of EGFR mutations in never-smokers and light smokers (≤15 pack-years) with adenocarcinoma of the lung is comparable.
- The expected EGFR mutation rate, based on the proposed demographic selection of patients, is approximately 30% for non-Asians and 50% for Asians. Based on our current feasibility assessment, we expect approximately equal proportion of Asian and non-Asian patients in the final trial population.
- Retrospective and prospective studies demonstrate that patients with the proposed demographic features (adenocarcinoma, never smoking or light smoking history) have a high incidence of EGFR mutations and are expected to gain more benefit when treated with an EGFR TKI.

FDA Response: This is a reasonable strategy to enrich the population. Depending on the outcome of the trial, it may be appropriate to further narrow the indication to patients with adenocarcinoma and the presence of activating EGFR mutations. Ultimately the indication will be a review issue.

Objectives

8.3 As noted in Question 8.2, enrollment of patients will be based on demographic features. Tumor samples for all patients will be tested for EGFR mutations. However, the randomization will not be stratified by EGFR status since the test results will be unavailable at the time of randomization.

One possible outcome of the trial would be a clear and substantial treatment effect among patients with mutations, accompanied by an ambiguous effect among patients without mutations. As an extreme, it might happen that the treatment effect is not even statistically significant among all randomized patients, but is dramatically positive among patients with mutations. Based upon the discussion in Sections 13.2 and 14.7, BI believes that a treatment effect that is both clinically and statistically significant, but which is restricted to those patients with confirmed EGFR mutation positive tumors, supports an approval in newly diagnosed patients with NSCLC whose tumors are positive for the EGFR mutation. The study design specifically identifies two primary analyses: all randomized patients and patients with EGFR mutation positive tumors. The primary analysis will be conducted on both populations with distribution of the alpha between the two populations. Does the Agency agree that the design of this study will support approval of BIBW 2992 for the treatment of the subset of patients with EGFR mutation in the event that the "all randomized patient" analysis is not statistically significant?

BI Rationale:

- There is a clear biologic rationale that identifies this sub-group.
- The sub-group of patients with confirmed EGFR mutation positive tumors is pre-specified and the Type I error has been conserved by apportionment.
- The observed effect in the sub-group is expected to be of sufficient magnitude to be considered unequivocal.

FDA Response: No.

We recommend stratifying the randomization by EGFR status using a fully specified analytically validated test.

Imbalances in baseline characteristics between treatment groups, particularly in the EGFR+ subgroup with relatively small sample size may introduce bias when comparing treatment arms within EGFR+ subgroup.

FDA believes it is essential that review and approval of the drug for indications dependent on the result of an EGFR mutation test shall be accompanied by review and approval of the EGFR mutation test as well. The materials received give no indication that you have developed an EGFR mutation test or arranged for another test developer

to submit for review and approval. Please address this issue. A host of questions (e.g., mutations analyzed, methodology, cut-point(s) for positive results and analytical validation plan) are outstanding. We recommend early discussions with CDRH concerning specification and analytical validation of the test.

DISCUSSION: The sponsor plans to contract with a third party to develop a diagnostic kit. Since the third party presumably will be submitting a PMA, the third party should request a meeting with CDRH to discuss diagnostic kit development. The meeting should include representatives from DDOP. The timing of this meeting should occur prior to submission of the SPA. Among the aims of the meeting should be development of a plan to include analytical validation of the assay before commencing the clinical trial and alignment of the clinical performance of the assay with the drug indication.

Comparators

8.4 As discussed in Section 14.3, there are no conclusive data to support the use of any platinum doublet chemotherapy regimen over another based on efficacy in the first-line treatment of patients with NSCLC. However, worldwide, there are both regional and institutional differences in the preferred first-line chemotherapy regimen for such patients.

BI proposes to restrict the choice of chemotherapy regimens in the comparator arm of Study 1200.32 to the two most widely used platinum-based regimens (gemcitabine-cisplatin or carboplatin-paclitaxel both administered for up to 6 cycles).

Does the Agency agree with this strategy for maintaining adequate control while accommodating global treatment preferences?

FDA Response: Restriction of the comparator arm to one of two regimens, gemcitabine-cisplatin or carboplatin-paclitaxel, would be satisfactory.

If the combination of pemetrexed-cisplatin gains wider acceptance as a standard chemotherapy regimen in the first-line treatment of NSCLC patients but has not received FDA approval for this indication, does the Agency agree that it would be acceptable to use this chemotherapy regimen in place of the gemcitabine-cisplatin chemotherapy regimen considering it is a platinum-based regimen with apparent efficacy results similar to current standards?

BI Rationale:

- There is considerable regional and institutional variation in the choice of first-line chemotherapy for patients with advanced NSCLC.

- There are no significant statistical or clinical differences between the two above-mentioned platinum-based doublet chemotherapy regimens in the first-line treatment of advanced NSCLC.
- Mandating one chemotherapy regimen for a large global lung cancer study could adversely affect patient recruitment.

FDA Response: Alimta was approved in September 2008 as first line therapy with cisplatin for non-squamous NSCLC. It would be acceptable to use this combination in place of gemcitabine-cisplatin.

Endpoints and Statistical Considerations

8.5 As discussed in Section 14.5, BI believes that progression-free survival (PFS) is an appropriate primary endpoint in the first-line NSCLC setting. The inherent difference in the randomisation arms (a tyrosine kinase inhibitor [TKI] versus chemotherapy) in Study 1200.32 will impact the choice of subsequent treatments with an inevitable imbalance, so that patients who progress after chemotherapy are more likely to receive a TKI, and vice versa. This unequal treatment distribution after disease progression is expected to obscure the effect of BIBW 2992 on overall survival. As a result, the analysis of overall survival will be principally descriptive. The planned statistical analyses will thoroughly describe the overall pattern of time to death, together with the extent and influence of post-progression treatment using all available information from a database of 1250 patients.

Does the Agency agree with BI's proposal to utilize PFS as the primary endpoint and the proposed strategy for analysing overall survival (see Section 14.6)?

BI Rationale:

PFS as Primary Endpoint

- The commercial availability of other EGFR TKI inhibitors will result in anti-cancer treatment after disease progression that is similar to the therapy that would be administered if patients were allowed to crossover to the opposite regimen after progression, thereby abating any potential overall survival advantage.
- PFS is not subject to the effect of subsequent treatment(s) after disease progression.
- The effect BIBW 2992 on PFS is expected to be of sufficient magnitude to be considered unequivocal.

Strategy for Analysing Overall Survival

- Regardless of the sample size, subsequent unequal treatment of patients after disease progression would be expected to eliminate any advantage of treatment with BIBW 2992 on overall survival. As a result, the analysis of overall survival will be principally descriptive.
- The analyses will describe thoroughly the overall pattern of time to death, together with the extent and influence of post-progression treatment. Although a variety of strategies will be employed to clarify the effect of BIBW 2992, no one analysis can be expected to be definitive.
- One of the goals of the analysis would be to identify any hint of a negative effect on overall survival. With a database of 1250 patients, the analyses will provide the clearest possible description of the effect of BIBW 2992 on overall survival.

FDA Response: In general, a substantial, robust improvement in PFS that is clinically meaningful and statistically persuasive, and has an acceptable risk-benefit profile may be considered for regulatory decision-making. However, you should be aware that PFS is subject to ascertainment bias and the results of the analysis may be influenced by any imbalance in assessment dates or missing data between treatment arms.

- **Progression events should be confirmed by blinded independent review if the study is unblinded or the blinding is unlikely to conceal the therapy.**
- **Also note that a statistically significant difference in PFS may not necessarily demonstrate a clinically meaningful difference.**
- **We discourage using interim results of PFS to make a claim of efficacy.**
- **Overall Survival should be considered as a secondary endpoint, or as a co-primary endpoint with alpha allocation.**

The study should be powered also for Overall Survival.

Overall Survival should be analyzed formally and not as an exploratory endpoint.

DISCUSSION: The sponsor will be revising the SAP along with the new protocol where the sponsor proposes to conduct the study only in the sub-population. The sponsor will not claim efficacy based on interim PFS analysis. OS will be a secondary endpoint and a planned analysis will be submitted.

8.6 As discussed in Section 14.7, the effect of BIBW 2992 on PFS will be tested twice: 1) among all randomized patients and 2) within the sub-group of patients whose tumors are positive for EGFR mutations. It is hypothesized that BIBW 2992 will improve PFS by 23% (6.5 months to 8.0 months) among all randomized patients, and by 54% (6.5 months to 10.0 months) among patients whose tumors are positive for EGFR mutations.

As noted in Question 8.3, the randomization will not be stratified by EGFR mutation status since test results will be unavailable at the time of randomization.

An overall Type 1 error of 0.025 (one-sided) will be split between the two hypotheses in proportion to the expected treatment effects for each comparison. One-sided alpha of 0.01525 will be allocated to the test among all randomized patients. For patients whose tumors are positive for EGFR mutations, alpha will be 0.00975, one-sided.
Does the Agency consider this statistical strategy of apportioning alpha to be appropriate, considering that success in patients whose tumors are positive for EGFR mutations might be a prerequisite for success in the overall population?

BI Rationale:

- Apportioning alpha to the two comparisons such that the sum equals 0.025 is conservative in two ways. First, the two hypothesis tests are positively correlated. Secondly, there is no reason to expect that the effect of BIBW 2992 might reach statistical significance among all randomized patients, while failing to do so among patients whose tumors are positive for EGFR mutations.

FDA Response: Please see the response to Question 8.3. Conclusions based on interim PFS analysis are not acceptable.

A problem with the proposed "split alpha" approach is that a significant overall drug effect could be driven by a large drug effect in the EGFR positive subgroup. This would pose a substantial review issue with regard to drug approval for the combined (EGFR mutation positive and EGFR mutation negative) population. An alternative to consider is a hierarchical approach of testing at level 0.05 for effect in the EGFR mutation positive subgroup, and if significant, testing at level 0.05 for effect in the EGFR mutation negative subgroup. If the effect is significant on both subgroups, then the drug can receive a claim for overall effect. The hierarchical testing approach preserves the type I error rate at 0.05.

Please note, to gain approval of the EGFR test as a predictive marker for selecting the drug, the drug effect should be larger in the EGFR positive subgroup than in the EGFR negative subgroup. That is, a statistically significant interaction between EGFR status and drug needs to be demonstrated. The interaction also needs to be clinically significant in magnitude to warrant selection of drug on the basis of the test.

8.7 As discussed in Section 14.7, the regional/institutional differences noted in Question 8.4 might cause the effect of BIBW 2992 to falsely appear to vary when compared with each of the two chemotherapy regimens, when, for example, the heterogeneity was caused by an imbalance in ethnicity (Asian versus non-Asian). The potential for imbalance is particularly acute within the

sub-group of patients whose tumors are positive for EGFR mutations because: 1) of the relatively small number of patients whose tumors are positive for EGFR mutations and (2) it is not possible to stratify by EGFR mutation status.

BI proposes not to distinguish between the two chemotherapy regimens in the proposed primary analysis. That is, the statistical model will include a binary effect for treatment (BIBW 2992 vs. control). In addition, BI will conduct exploratory analyses examining the effect of BIBW 2992 when compared with each of the chemotherapy regimens separately.

Does the Agency agree that these two chemotherapy regimens can be assumed to be similarly effective for purposes of the primary analysis? If the Agency does not agree with the proposed approach, BI would greatly appreciate any insights for refining the primary statistical analysis in light of these confounding effects.

BI Rationale:

- The primary test of interest is BIBW 2992 vs. control.
- If the evidence in the medical literature is sufficient to consider the two control regimens equally effective, such an a priori assumption would allow the analysis to test the primary hypothesis directly, without interference of imbalance or confounding associated with the selection of chemotherapy regimen.

FDA Response: Clinically, it is acceptable to assume similar effectiveness of the two chemotherapy regimens. See response to question 8.4.

CLINICAL DEVELOMENT STRATEGY FOR APPROVAL

The clinical development plan for BIBW 2992 is intended to support the following proposed indication (see Section 3):

BIBW 2992 is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) (b) (4)

8.8 (b) (4)

(b) (4) Does the Agency agree that one adequate and well-controlled pivotal study would be sufficient for registration to support the proposed indication?

BI Rationale:

- It is assumed at the time of regulatory action, BIBW 2992 has received approval for the treatment of patients with locally advanced or metastatic NSCLC (b) (4)
- The anticipated magnitude of improvement in PFS (i.e., primary endpoint) is considerable.
- Conducting two trials in the same setting considering the recruitment challenges will be difficult.

FDA Response: (b) (4)

CLINICAL PHARMACOLOGY

8.9 Considering the available pharmacokinetic (PK) data in NSCLC patients and the anticipated BIBW 2992 PK data that will be available at the time of submission from ongoing/completed Phase I-III studies in patients with breast cancer, head and neck squamous cell carcinoma and glioblastoma patients (see Section 16.6), BI believes that it is not necessary to perform PK sampling in Study 1200.32. Does the Agency agree?

BI Rationale:

- PK data that is anticipated to be available at the time of submission includes analyses from approximately 720 patients treated with BIBW 2992 monotherapy. The anticipated data are as follows:
  - Data from approximately 540 patients with NSCLC from studies 1200.22 (Phase II, planned, N=120), 1200.23 (Phase IIb/III, planned, N=267), 1200.39 (Phase II, planned, N=50), 1200.40 (Phase II, planned, N=70) and 1200.41 (Phase II, planned, N=40)
  - 40 Head and Neck Squamous Cell Cancer (HNSCC) patients from Study 1200.28 (Phase II trial ongoing)
  - 40–70 glioblastoma patients from Study 1200.36 (Phase II trial initiated in July 2008)
  - 100 Breast Cancer (BC) patients from studies 1200.10 and 1200.11 (Phase II ongoing trials)
- PK data from approximately 123 patients with various advanced solid tumors treated with BIBW 2992 monotherapy are currently available from completed Phase I studies (1200.1, 1200.2, 1200.3 and 1200.4).
- Exposure-response correlations will be available from the ongoing Phase IIb/III 1200.23 trial based on 267 patients treated with BIBW 2992 monotherapy at the time of submission.

FDA Response: We note your plan for a population PK analysis using data from another US phase 2b/3 trial (1200.23) in patients with NSCLC, and this appears to be the only Phase 3 trial for which you plan to have PK samples. We recommend that you collect sparse plasma sampling during your proposed pivotal phase 3 trial (1200.32) to further attempt to characterize the various PK/PD relationships associated with efficacy and toxicity in the target population. Exposure-response information linking dose, concentration, and response can support dosage adjustments in patients where pharmacokinetic differences are expected or observed to occur because of one or more intrinsic or extrinsic factors. In addition, sparse PK sampling in the proposed phase 3 trial will help explain variability by identifying factors of demographic, pathophysiological, environmental, or concomitant drug-related origin that may influence the pharmacokinetic behavior of a drug. Please refer to the guidance for industry entitled "Exposure Response Relationships" at http://www.fda.gov/cder/guidance/5341fnl.pdf for more information.

8.10 Section 16.7 of this briefing package discusses the anticipated PK data expected to be available at the time of submission, including the relevant covariates. BI does not believe it is necessary to perform distinct trials in special patient populations (e.g. elderly, ethnic origin, renal-, or hepatic-impaired patients) based on the anticipated PK data, including the relevant covariates that will be available at the time of submission. Does the Agency agree?

BI Rationale:

- See BI rationale for Question 8.9 above.
- BI plans to perform a correlation plot analysis or covariate analysis based on the pooled data of trials (preferably trials 1200.22, 1200.23 and if feasible in combination with 1200.10, 1200.11, 1200.28, 1200.36, 1200.39, 1200.40 and 1200.41) to investigate the influence of e.g. sex, age (elderly), race (ethnic origin), creatinine clearance (mild/moderate renal impaired patients) as well as liver enzymes elevations e.g. AST, ALT, γGT (mild/moderate hepatic-impaired patients) on the PK characteristics of BIBW 2992.

FDA Response: Your mass-balance study indicates that > 80% of recovered BIBW2992 is excreted in the feces. Therefore, a dedicated study in patients with impaired hepatic function would be important in order to provide dosing recommendations in this patient population. Your plan to assess how hepatic impairment affects the PK of your drug appears to describe a "reduced study design" described in the guidance for industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function" that can be found at http://www.fda.gov/cder/guidance/3625fnl.pdf. We recommend that you use the information within this guidance to develop your plan for assessing the effect of hepatic impairment on the PK of BIBW2992.

8.11 Reference is made to the November 27, 2006 pre-meeting comments that BI received in preparation for the EOP 1 second-line NSCLC meeting scheduled for December 1, 2006. At this time, the Agency advised BI to conduct *in vivo* drug-drug interaction studies with ketoconazole and rifampicin. Section 16.8 describes the additional data that has become available since the above-referenced feedback from both *in vitro* and *in vivo* studies that demonstrate BIBW 2992 metabolism via CYP450 (especially CYP3A4) enzymes is of a subordinate role. Based on these additional data, BI does not believe that it is necessary to conduct distinct clinical drug-drug interaction studies with BIBW 2992 together with ketoconazole or rifampicin or with other CYP450 enzyme inducer or inhibitor. Does the Agency agree?

BI Rationale:

BIBW 2992 as a CYP450 substrate:

- Results from a human [^{14}C] Absorption, Distribution, Metabolism and Excretion (ADME) trial, demonstrate that metabolism is of a subordinate role for BIBW 2992 and that enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of BIBW 2992 *in vivo.*
- Only approximately 2% of the dose were metabolised by FMO3 *in vivo*. The CYP3A4-dependent N-demethylation was even too low to be quantitatively detected in human volunteers. Therefore, intrinsic (e.g. genetic predisposition) or extrinsic (e.g. by comedications) effects on the activity of FMO3 or CYP3A4 *in vivo* will be of little, if any, relevance for the pharmacokinetics of BIBW 2992.
- A large preponderance of Michael adducts of BIBW 2992 to protein, cysteine, glutathione, etc. were found to be the main metabolite of BIBW 2992 *in vivo.*
- The human ADME data confirmed the results of the preclinical [^{14}C] ADME studies and all metabolites of the human [^{14}C] ADME study were observed in the rat or the minipig.

BIBW 2992 as a CYP450 inhibitor:

- BIBW 2992 at concentrations up to 100 µM did not show potent inhibition of the cytochrome P450 isoenzymes that are most relevant for drug metabolism in human (1A1/2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 4A11).

BIBW 2992 as a CYP450 inducer:

- BIBW 2992 was dosed to rats, liver microsomes were prepared and investigated for parameters of enzyme induction. No signs of enzyme induction were found in terms of liver to body weight ratios, microsomal

hepatic protein concentration, hepatic content of total cytochrome P-450 or enzyme activities of CYP1A, CYP2B, CYP3A, CYP2E1 and CYP4A.

FDA Response: If < 25% of the metabolism of your drug is via the CYP3A4 route, this is acceptable. However, based upon the amount of unrecovered 14C in your human mass balance study, and the possibility that CYP3A4 forms metabolites other than the N-desmethyl metabolite (ml0), this conclusion is improbable. Thus, we continue to recommend clinical drug-drug interaction studies with BIBW 2992 together with ketoconazole and rifampicin. Your *in vivo* data to assess P450 induction are from studies in rats. You will need to screen your drug *in vitro* to assess whether it is an inducer of human CYP450s. This will help determine the potential for *in vivo* drug-drug interactions and the need for *in vivo* metabolic drug-drug interaction studies to evaluate CYP450 induction. Please see the Drug-Drug Interaction website and relevant guidances at http://www.fda.gov/cder/drug/drugInteractions/default.htm.

DISCUSSION: The *in vitro* induction studies are ongoing.

8.12 As discussed in Section 16.9, clinical data, to date, and data from *in vitro* studies demonstrate that BIBW 2992 is a P-gp substrate and inhibitor. However, considering the sum of these data, BI does not believe that it is necessary to conduct distinct P-gp drug-drug interaction studies with BIBW 2992. Does the Agency agree?

BI Rationale:

BIBW 2992 as a P-gp inhibitor:

- *In vitro* data demonstrate a concentration-dependent inhibition of P-gp through BIBW 2992. The IC_{50} of BIBW 2992 is 1.59 µM, indicating BIBW 2992 as only a medium potent P-gp inhibitor.
- Even the highest individual BIBW 2992 maximum plasma concentration observed to date (100 ng/ml corresponding to 0.21µM) at the Maximum Tolerated Dose (MTD) is substantially below the possible threshold needed for a significant clinical interaction to occur.
- BIBW 2992 dosed sequentially with other P-gp substrates (e.g. docetaxel in Study 1200.6) demonstrated no clinically relevant influence of BIBW 2992 on the PK of docetaxel.
- Preliminary data of BIBW 2992 dosed concomitantly with BIBF 1120, another BI investigational drug (b) (4) that is also a P-gp substrate, displays no influence of BIBW 2992 on the PK of BIBF 1120 in a concomitant administration setting.

BIBW 2992 as a P-gp substrate:

- *In vitro* data demonstrate that BIBW 2992 is a P-gp substrate. The affinity of BIBW 2992 for human P-gp could not be assessed precisely, however,

- Even the highest individual BIBW 2992 maximum plasma concentration observed to date (100 ng/ml corresponding to 0.21µM) at the MTD is substantially below the possible threshold needed for a significant clinical interaction.
- Preliminary data of BIBW 2992 dosed concomitantly with BIBF 1120 (BI investigational agent [redacted] (b) (4)), a medium to weak potent P-gp inhibitor with a K_i expected to be above >30 µM, displayed no influence of BIBF 1120 on the PK of BIBW 2992 in a concomitant administration setting.

FDA Response: Based on the data provided in this submission, the estimated I/IC50 ratio for P-gp inhibition is > 0.1 (0.21 µM /1.59 µM = 0.13). This suggests that the possibility of a drug-drug interaction is not "remote". It is difficult to evaluate the adequacy of your in vivo drug-drug interaction studies with uncharacterized or weak P-pg substrates (BIBF 1120 and docetaxel). Drug-drug interaction studies to evaluate *in vivo* inhibition of P-gp by your drug should be done with known prototype substrates for P-gp and include known/established positive controls. Please see the Drug-Drug Interaction website and relevant guidances at http://www.fda.gov/cder/drug/drugInteractions/default.htm.

If 25% or less of clearance is via P-gp transport, an in vivo study of the effects of inhibitors on the PK of your drug will not be needed. However, the current data summary does not allow us to conclude that this is the case. Thus, we recommend you study the effect of P-gp inhibition on the pharmacokinetics of your drug.

DISCUSSION: The sponsor proposed to calculate the Ki using an appropriate model to further assess the P-gp inhibition *in vitro*. The results of these studies will be provided upon completion.

8.13 As discussed in Section 16.10, there are BIBW 2992 PK data that demonstrate no deviation from "dose proportionality". Based on these data, BI is not planning to conduct a distinct dose proportionality study with BIBW 2992. Does the Agency agree?

BI Rationale:

- Data from four Phase I BIBW 2992 monotherapy trials (1200.1, 1200.2, 1200.3 and 1200.4) in patients with advanced solid tumors provide no evidence for a deviation from a dose proportional increase in AUC and C_{max} of BIBW 2992 either after single dose or at steady state (range 10 mg to 100 mg once daily dosing). This observation was observed via visual inspection.

- A preliminary population PK analysis of trials 1200.1, 1200.2 and 1200.3 demonstrated no sign of a study or dose-specific difference and no time-dependency of BIBW 2992 PK.
- BIBW 2992 displayed high inter-patient variability in PK parameters in all completed trials, which prevented a formal statistical testing of dose-proportionality.
- Data from trials (1200.6 and 1200.20) in which BIBW 2992 was dosed sequentially with chemotherapy (i.e., docetaxel), demonstrated that there was no evidence of "non-dose proportionality" of BIBW 2992 PK characteristics in a dose range from 10 mg to 160 mg BIBW 2992 (once daily dosing).

FDA Response: Your plan not to conduct a distinct dose proportionality study appears acceptable from a clinical pharmacology perspective.

8.14 As discussed in Section 16.11, the results from a food effect study conducted in patients with advanced solid tumors treated with 40 mg of BIBW 2992 daily, demonstrated that there is a food effect with BIBW 2992. Since the maximum tolerated dose (MTD) for BIBW 2992 has been defined as 50 mg daily and BIBW 2992 is administered without food, BI believes that it is not necessary to conduct an additional food effect study with BIBW 2992 at the MTD (50 mg) for regulatory purposes. Does the Agency agree?

BI Rationale:

- PK evaluation in the food effect study (1200.3) demonstrated a statistically significant food effect with decreased BIBW 2992 plasma concentrations after food intake of a high fat, high caloric breakfast.
- BIBW 2992 gMean C_{max} and $AUC_{0-\infty}$ values decreased around 50% and 39%, respectively under fed conditions compared to fasted conditions and for both PK parameters the 90% confidence interval was outside the acceptance range of 80-125%. This indicated that BIBW 2992 plasma concentrations under fed conditions are not bioequivalent to the ones under fasted conditions.
- In Study 1200.3 BIBW 2992 was dosed to patients with various advanced solid tumors at a dose of 40 mg once daily, which was considered as the MTD of BIBW 2992 monotherapy at start of the food effect arm of this trial.
- Based on the data above, BIBW 2992 will only be administered in the fasted state.
- BI does not expect a different food effect of BIBW 2992 with the final evaluated MTD dose of 50 mg BIBW 2992 and is therefore not planning a separate food effect trial with 50 mg BIBW 2992 in cancer patients.

FDA Response: Your plan to assess a food effect appears acceptable from a clinical pharmacology perspective.

8.15 As discussed in Section 16.12, BI is planning to conduct a relative bioavailability study comparing the Phase II BIBW 2992 tablet formulation to the Phase III/final to-be-marketed formulation (note: the to-be-marketed and Phase III formulations are the same). In addition, BI is collecting limited pharmacokinetic (PK) data from the ongoing Phase III third-line or fourth-line NSCLC clinical trial (1200.23) which is utilizing the Phase III formulation of BIBW 2992.

The qualitative and quantitative differences in the formulations of the film-coated tablets used in Phase II and Phase III (to-be-marketed) film-coated tablets are minor, as shown in Tables 16.12:1 and 16.12:2 of the briefing information. BI believes that specific *in vivo* bioequivalence (BE) studies are not required to bridge the change in formulations from the Phase II tablets to the Phase III (to-be-marketed) tablets. Does the Agency agree?

BI Rationale:

- See Section 16.12.

FDA Response: The 4 different strengths of the phase III clinical trial formulations do not meet any of the definitions of proportionally similar. If the plasma levels resulting from these 4 strengths are appropriately characterized, then further relative bioavailability studies may not be needed. However, if plasma levels in the phase 3 clinical trials are obtained on only some of the strengths, then the relative bioavailability of the remaining strengths will need to be determined.

DISCUSSION: The Agency assessed that the changes from the phase 2 to the phase 3 formulation is considered a level 3 change. Therefore, according to FDA guidances we require a bioequivalence study. Given that the phase 3 trial will be conducted with the final market image product, a formal bioequivalence study is not necessary. The Agency, however, requested the sponsor to provide full pharmacokinetic profiles of all dosage strengths used in the phase 3 trial. In addition, the food effect information gathered from their earlier study should be bridged to the new formulation.

Additional Comments:

Statistical

- **The trial should not be stopped for efficacy at any of the interim PFS analyses.**

- **Patient reported outcomes are subject to bias in an open label study and will be considered exploratory.**

CMC

- **Comparative test data on drug product batches from both Phase II and Phase III/to-be-marketed using same specification. Identify any new impurities that are observed at release and at stability.**
- **Provide comparative stability test data to bridge between drug products from Phase II and Phase III/to-be-marketed formulation.**
- **Comparative in vitro dissolution for drug product from Phase II and Phase III/to-be-marketed formulations. Any other change (e.g. manufacturing, analytical methods) for new formulation and strength should be indicated.**

CDRH believes it will be important to understand mutation specificity for the drug action, receptor specificity for the drug action and the specific mutations that are relevant to the drug's action.

ACTION ITEMS: None.

_____
Milinda F. Vialpando
Project Manager

Concurrence Chair:_____
Ann Farrell, M.D.
Deputy Division Director &
Medical Team Leader

Study 1200.32 was designed to demonstrate superiority of BIBW 2992 over standard chemotherapy in a demographically selected population of patients with NSCLC based on smoking history. To show this, the assumption in the protocol was that the efficacy of BIBW 2992 would be comparable to chemotherapy in patients with EGFR wild type (non-mutated) or EGFR mutation status unknown (~70% of the whole population of the trial). This assumption was based on published data suggesting efficacy of EGFR TKIs in EGFR wild type NSCLC.

The recently presented results of the IPASS trial (ESMO, September 2008[1]) challenge this assumption. In the IPASS trial (i.e., randomised trial of gefitinib versus chemotherapy in Asian light or never smokers with adenocarcinoma of the lung in which PFS was the primary endpoint) which evaluated a similar population to BI's proposed trial (1200.32), gefitinib was shown to be superior to chemotherapy in patients who had EGFR mutations. In the absence of EGFR mutations, gefitinib was inferior to chemotherapy. The results of IPASS strongly indicate that EGFR mutational status is the prevailing predictive marker of efficacy of EGFR TKIs.

Based on the above, we have decided to modify the eligibility criteria of Study 1200.32 to include only patients with EGFR mutations which will result in a considerably smaller study. In light of the recent FDA approval of pemetrexed/cisplatin and the reduced size of the proposed study, we are also considering the use of pemetrexed/cisplatin as the only comparator chemotherapy regimen.

The main features of the revised trial design are outlined below:

Eligibility criteria:	Stage IIIB/IV adenocarcinoma of lung harbouring EGFR activating mutation
Treatment:	BIBW 2992 vs Pemetrexed/Cisplatin; 2:1 randomization
Primary endpoint:	Progression Free Survival (PFS) 11 months vs. 7 months (HR 0.64)
Sample size:	~ 330 patients

It is our intention to discuss the revised protocol during a Special Protocol Assessment request that will be submitted following the EOP 2 meeting. We plan to include questions similar to those outlined in the briefing package (dated September 10, 2008/SN 0259) with a focus on the proposed design described above.

[1] Annals of Oncology 19 (Supplement 8): viii1-viii4, 2008 doi: 10.1093/annonc/mdn649

Linked Applications	Sponsor Name	Drug Name
IND 67969	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	BIBW-2992 MA2

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANN T FARRELL
10/16/2008

MID-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

LATE CYCLE MEETING MINUTES

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor
Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Please refer to your New Drug Application (NDA) dated November 14, 2012, received November 15, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Afatinib tablets, 20 mg, 30 mg, 40 mg, (b) (4)

We also refer to the Late-Cycle meeting (LCM) meeting between Boehringer Ingelheim and the FDA on May 7, 2013. A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Deanne Varney, Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Late-Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Date and Time: May 7, 2013, 2:30PM
Application Number: NDA 201292
Product Name: Afatinib
Proposed Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test
Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

FDA ATTENDEES

Richard Pazdur, MD	Office Director, OHOP
Patricia Keegan, MD	Division Director, DOP2/OHOP
Tamy Kim, PharmD	Associate Director, Regulatory Affairs, OHOP
Anthony Murgo, MD	Cross-Discipline Team Leader, DOP2/OHOP
Gideon Blumenthal, MD	Clinical Team Leader, DOP2/OHOP
Shakun Malik, MD	Clinical Reviewer, DOP2/OHOP
Jun Yang, PhD	Clinical Pharmacology Reviewer, DCP5/OCP/OTS
Runyan Jin, PhD	Clinical Pharmacology Reviewer, DCP5/OCP/OTS
Hong Zhao, PhD	Clinical Pharmacology Team Leader, DCP5/OCP/OTS
Jonathan Norton, PhD	Statistical Reviewer, OB/DBV
Rosane Charlab Orbach, PhD	Genomics Reviewer, OMPT/CDER/OTS/OCP/Genomics
Dubravka Kufrin, PhD	Nonclinical Reviewer, DHOT/OHOP
Whitney Helms, PhD	Nonclinical Team Leader, DHOT/OHOP
Li Shan Hsieh, PhD	CMC Reviewer, ONDQA
Ali Al Hakim, PhD	CMC Branch Chief, ONDQA
Elsbeth Chikhale, PhD	Biopharmaceutics Reviewer, ONDQA
Deanne Varney	Regulatory Project Manager, DOP2/OHOP
Jennifer Shen, PhD	PMA Lead Reviewer, CDRH/OIR/DIHD
Yun-Fu Hu, PhD	Branch Chief, CDRH/OIR/DIHD
Reena Philip, PhD	Deputy Division Director, CDRH/OIR/DIHD
Mahesh Ramanadham, PharmD	Acting Team Leader, DGMPA/OMPQ
David Doleski	Director, DGMPA/OMPQ
Mary Farbman	Facilities Reviewer, DIDQ/OMPQ
Carmelo Rosa, PsyD	Division Director, DIDQ/OMPQ
Andrea Chamblee, JD	Branch Chief, DIDQ/OMPQ
Joy Sharp, JD	Senior Regulatory Counsel, OC
Quynh-Van Tran, PharmD	Regulatory Review Officer, OPDP
Lauren Iacono-Connors, PhD	Reviewer, DGCPC/OSI

(b) (4)

APPLICANT ATTENDEES

Chris Corsico, MD	Head of Corporate Division Quality, Regulatory, Pharmacovigilance and Epidemiology
Sabine Luik, MD, MBA	Sr. Vice President, Medicine & Regulatory Affairs, US Regional Medical Director, North America
Mehdi Shahidi, MD	Leader Clinical Development Afatinib
Victoria Zazulina, MD	Leader Clinical Development Afatinib NSCLC
Dennis O'Brien, MD	Team Member, Drug Safety
James Love, M. Stat.	Project Statistician
Gerhard Koeller	Corporate Quality
Gerhard Gigl	Launch and Production Site, Germany
Mark Edmonds	Quality Assurance
Robert Fromuth	Corporate Senior Vice President, Established Products
Thorsten Laux, PhD	Global Regulatory Affairs Manager
Pamela Strode	Executive Director, Regulatory Affairs
Ann Agnor, MS	Regulatory Affairs US
Rainer Kleemann, Dr. med. vet.	International Project Leader

INTRODUCTION

The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues, Advisory Committee (AC) meeting plans (if scheduled), and the objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application.

During the meeting, we may discuss additional information that may be needed to address the identified issues, whether it will be reviewed by the Agency in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. If you submit any new information in response to the issues identified in this briefing package prior to this LCM or the Advisory Committee meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

DISCUSSION OF SUBSTANTIVE REVIEW ISSUES

Clinical and Statistical Issues:

1. (b) (4)

Study 1200.23 (Lux Lung 1) was a Phase IIb/III randomized double-blind trial of afatinib plus best supportive care (BSC) versus placebo plus BSC in non-small cell lung cancer patients who had failed erlotinib or gefitinib and had previously received 1 or 2 lines of chemotherapy. The trial enrolled 585 patients who were randomized (2:1) to receive 50 mg afatinib orally once daily plus best supportive care (n=390) or placebo plus BSC (n=195).

The trial population was clinically enriched for EGFR mutations by requiring patients to have had prior EGFR-TKI therapy for at least 12 weeks. In the study 186/585(32%) of the patients had tissue available for EGFR mutational status testing at either the local lab or central lab. There was a high degree of imbalance between the two arms on this retrospective analysis of EGFR mutation status with a high degree of discrepancy noted between the types of EGFR mutations reported by the central lab verses the local lab.

The study failed its primary endpoint of OS with the median OS for placebo of 12.0 months and afatinib of 10.8 months (HR=1.08; 95% confidence interval: 0.86 to 1.35).

(b) (4) The study failed its primary endpoint of OS, had a marginal PFS benefit as secondary endpoint, and the population is poorly defined.

Discussion During Meeting: BI expressed their understanding of this issue. No further discussion occurred.

2. (b) (4)

In the study, of the patients treated with afatinib with a starting dose of 40 mg po per day:

- Only 16/230 patients were dose escalated to 50 mg
- Of the 16 patients, 13 received afatinib 50 mg for 21 days or more, 10/16 patients needed at least one dose reduction and 5/10 needed 2 dose reductions.

In addition, in the supportive study 1200.22 (Lux Lung 2), an open-label, single-arm trial, the two starting doses of 40 mg and 50 mg showed a similar objective response for 40 and 50 mg doses and increased incidence and severity of adverse events with the 50 mg dose.

Discussion During Meeting: BI expressed their understanding of this issue. No further discussion occurred.

3. (b) (4).

The pharmacology data submitted to support the mechanism of action statement in the proposed label was very limited in regards to the *in vitro* or *in vivo* effects of afatinib on inhibition of either common or rare EGFR mutations.

In pivotal study 1200.32 the majority of the patients enrolled had a tumor sample with an EGFR mutation categorized as either Exon 19 deletion [170/345(49%)] or Exon 21 (L858R) [138/345(40%)] while a small number [37/345(11%)] were of the "Other" mutation category. This small cohort of 10 different genetic subtypes were distributed in an unbalanced way in afatinib (N=26) and chemotherapy (N=11) treatment groups.

On exploratory efficacy results analyses in the study by EGFR mutation within the pre-specified subgroup of patients with 'common' EGFR mutations [i.e., Exon 19 deletion or Exon 21 (L858R) mutation], the benefit seems to be driven by the Exon 19 deletion subgroup while in patients with "Other" mutation category there seems to be a possible detrimental effect on PFS and OS.

Therefore, the indication for afatinib will be limited to patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Question to BI: What studies are ongoing or planned to evaluate efficacy in NSCLC patients whose tumors harbor uncommon EGFR mutation(s)?

Discussion During Meeting: BI does not have any planned or ongoing studies to evaluate the efficacy of afatinib in NSCLC patients with uncommon EGFR mutations.

(b) (4)

(b) (4)

Chemistry, Manufacturing, and Controls and Facility Issues:

4. BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG was inspected by the FDA from November 5, 2012 through November 12, 2012. This site is listed as the site of drug substance and drug product manufacturing. At the conclusion of this inspection, our field investigator conveyed deficiencies to the representative of the facility. The review of the responses received between November 2012 and February 28, 2013 to the FDA form 483 issued at the close of this inspection is ongoing. At this time a final compliance status has not been determined. FDA reminds BI that, per 21 U.S.C. 505 (d)(3), grounds for denying approval of a pending application include finding the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity. CDER/OC/OMPQ/Division of International Drug Quality will communicate the final status of its review of BI's response as soon as possible.

   Discussion During Meeting: BI acknowledged receipt of the Warning Letter on Monday, May 6, 2013, and noted that they are working to respond to the issues outlined in the letter.

   FDA stated that the findings from the November 2012 inspection were significant, and encouraged BI to respond to the Warning Letter within 15 days. FDA believes the issues in the warning letter can be resolved, but BI must provide FDA with an assurance that the facility can and will operate at a level the agency is comfortable with.

   BI noted that they are aware that the issues are serious and must be resolved. BI thought they had interpreted the corrective actions appropriately, but acknowledged that they now understand that the issues have not been resolved. BI stated that they intend to respond to the Warning Letter within 15 days.

   BI inquired if it would be appropriate to reach out to the Office of Compliance after their response is submitted, and FDA stated that this would be acceptable.

   FDA noted that BI should point out any changes that will impact other facilities, in addition to the facility that was inspected. BI stated that they have implemented a global corrective action plan, and that there have been organizational changes and changes in governance.

   The Office of Compliance and BI will hold an additional teleconference to discuss this issue in further detail.

Companion Diagnostic:

5. Safe and effective use of afatinib requires the approval of a companion diagnostic to identify specific EGFR mutations. There are outstanding issues and information requests for the companion diagnostic test which will need to be addressed prior to approval.

   Discussion During Meeting: BI noted that they are in continual contact with Qiagen, and that the response to the information request is on track.

DISCUSSION OF POST-MARKETING REQUIREMENTS AND COMMITMENTS

6. Post-Marketing Commitment: To submit the data from the final overall survival analysis from Study 1200.32 in order to better characterize the effects of afatinib treatment on overall survival. Final submission date: 3/31/2014.

   Discussion During Meeting: BI noted that the formal full clinical trial report will be available in April 2014. It was decided to extend the final submission date to 4/30/2014 in order to allow for submission of the complete clinical trial report.

DISCUSSION OF LABELING ISSUES

7. Indication statement and limitation of use: FDA believes a limitation of use is appropriate given the small number of patients tested and apparent decrease in both progression free and overall survival in afatinib treated patients with "other" EGFR mutations.

   Discussion During Meeting: BI expressed that there will always be a small number of patients for whom safety and efficacy have not been established. BI accepts that the statement "Safety and efficacy of BRAND have not been established in patients whose tumors have other EGFR mutations" is included in the indication statement in the PI, but inquired if it must be introduced with the "limitation of use" terminology. FDA noted that per guidance and policy, this must be noted as a limitation of use.

   BI stated that their interpretation of a limitation of use is that there is a lack of effect. FDA stated that as currently worded in the PI, it is clear that the safety and efficacy have not been established, and that it is not intended as a contraindication.

   FDA noted that if BI can provide a compelling reason that this limitation of use would prevent use in necessary patient populations, FDA might revisit the issue.

   FDA noted that the issue will be discussed further internally.

DISCUSSION OF ADDITIONAL ISSUES

8. BI acknowledged that the indication statement is now specific for the exon 19 deletion and exon 21 substitution mutations. BI noted that in their counterproposal submitted on April 26, 2013, they included additional information regarding the intended patient population. BI inquired if the common mutation Kaplan-Meier curves can be included in the PI.

   FDA noted that a table was proposed, and is a concise way to present information that the Kaplan-Meier curve would not include in as much detail. FDA inquired if BI wants to present an integrated analysis for the intended population, and BI responded 'yes'.

   BI noted that all of the data can be summarized in a forest plot, if an additional column is included for the medians. BI will send the proposed revised forest plot for FDA review.

9. BI acknowledged that specific information for uncommon mutations is included in the PI. BI noted that that in their counterproposal submitted on April 26, 2013, they edited this information (b) (4). FDA stated that (b) (4) duration of response will be included in the PI.

10. BI noted that in their counterproposal submitted on April 26, 2013, they proposed to (b) (4)

(b) (4)

FDA will discuss this issue further internally.

ACTION ITEMS

Boehringer Ingelheim:

1. BI will work on a response to the Warning Letter, and will discuss in further detail with the Office of Compliance.

2. BI will send a proposed forest plot including data for the common mutations, including medians.

FDA:

3. FDA will discuss the Limitation of Use statement internally.

4. FDA will discuss the potential inclusion (b) (4) in the PI, (b) (4)

DECISIONS:

1. The final submission date for the PMC will be extended to April 30, 2014, to allow for submission of the complete clinical trial report.

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/s/

DEANNE R VARNEY
05/16/2013

PATRICIA KEEGAN
05/16/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

LATE CYCLE MEETING BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor
Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Please refer to your New Drug Application (NDA) dated November 14, 2012, received November 15, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Afatinib tablets, 20 mg, 30 mg, 40 mg, (b) (4)

We also refer to the Late-Cycle meeting (LCM) meeting scheduled for May 7, 2013. Attached is our briefing package, including our agenda for the upcoming meeting.

If you have any questions, call Deanne Varney, Regulatory Project Manager, at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Late-Cycle Meeting Briefing Package
Form FDA 483 – Issued 11/12/2012

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

LATE-CYCLE MEETING BRIEFING PACKAGE

Meeting Date and Time: May 7, 2013, 2:30PM
Application Number: NDA 201292
Product Name: Afatinib
Proposed Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test
Sponsor/Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.

INTRODUCTION

The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues, Advisory Committee (AC) meeting plans (if scheduled), and the objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues, whether it will be reviewed by the Agency in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. If you submit any new information in response to the issues identified in this briefing package prior to this LCM or the Advisory Committee meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

CURRENT SUBSTANTIVE REVIEW ISSUES

Clinical and Statistical Issues:

1. (b) (4)

Study 1200.23 (Lux Lung 1) was a Phase IIb/III randomized double-blind trial of afatinib plus best supportive care (BSC) versus placebo plus BSC in non-small cell lung cancer patients who had failed erlotinib or gefitinib and had previously received 1 or 2 lines of chemotherapy. The trial enrolled 585 patients who were randomized (2:1) to receive 50 mg afatinib orally once daily plus best supportive care (n=390) or placebo plus BSC (n=195).

The trial population was clinically enriched for EGFR mutations by requiring patients to have had prior EGFR-TKI therapy for at least 12 weeks. In the study 186/585(32%) of the patients had tissue available for EGFR mutational status testing at either the local lab or central lab. There was a high degree of imbalance between the two arms on this retrospective analysis of EGFR mutation status with a high degree of discrepancy noted between the types of EGFR mutations reported by the central lab verses the local lab.

The study failed its primary endpoint of OS with the median OS for placebo of 12.0 months and afatinib of 10.8 months (HR=1.08; 95% confidence interval: 0.86 to 1.35).

(b) (4)

. The study failed its primary endpoint of OS, had a marginal PFS benefit as secondary endpoint, and the population is poorly defined.

2. (b) (4)

In the study, of the patients treated with afatinib with a starting dose of 40 mg po per day:

- Only 16/230 patients were dose escalated to 50 mg
- Of the 16 patients, 13 received afatinib 50 mg for 21 days or more, 10/16 patients needed at least one dose reduction and 5/10 needed 2 dose reductions.

In addition, in the supportive study 1200.22 (Lux Lung 2), an open-label, single-arm trial, the two starting doses of 40 mg and 50 mg showed a similar objective response for 40 and 50 mg doses and increased incidence and severity of adverse events with the 50 mg dose.

3. (b) (4) .

The pharmacology data submitted to support the mechanism of action statement in the proposed label was very limited in regards to the *in vitro* or *in vivo* effects of afatinib on inhibition of either common or rare EGFR mutations.

In pivotal study 1200.32 the majority of the patients enrolled had a tumor sample with an EGFR mutation categorized as either Exon 19 deletion [170/345(49%)] or Exon 21 (L858R) [138/345(40%)] while a small number [37/345(11%)] were of the "Other" mutation category. This small cohort of 10 different genetic subtypes were distributed in an unbalanced way in afatinib (N=26) and chemotherapy (N=11) treatment groups.

On exploratory efficacy results analyses in the study by EGFR mutation within the pre-specified subgroup of patients with 'common' EGFR mutations [i.e., Exon 19 deletion or Exon 21 (L858R) mutation], the benefit seems to be driven by the Exon 19 deletion subgroup while in patients with "Other" mutation category there seems to be a possible detrimental effect on PFS and OS.

Therefore, the indication for afatinib will be limited to patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations.

Chemistry, Manufacturing, and Controls and Facility Issues:

4. BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG was inspected by the FDA from November 5, 2012 through November 12, 2012. This site is listed as the site of drug substance and drug product manufacturing. At the conclusion of this inspection, our field investigator conveyed deficiencies to the representative of the facility. The review of the responses received between November 2012 and February 28, 2013 to the FDA form 483 issued at the close of this inspection is ongoing. At this time a final compliance status has not been determined. FDA reminds you that, per 21 U.S.C. 505 (d)(3), grounds for denying approval of a pending application include finding 'the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity.' CDER/OC/OMPQ/Division of International Drug Quality will communicate the final status of its review of BI's response as soon as possible.

Companion Diagnostic:

5. Safe and effective use of afatinib requires the approval of a companion diagnostic to identify specific EGFR mutations. There are outstanding issues and information requests for the companion diagnostic test which will need to be addressed prior to approval.

POST-MARKETING REQUIREMENTS AND COMMITMENTS

6. Post-Marketing Commitment: To submit the data from the final overall survival analysis from Study 1200.32 in order to better characterize the effects of afatinib treatment on overall survival. Final submission date: 3/31/2014.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

CURRENT ASSESSMENT OF NEED FOR REMS OR OTHER RISK MANAGEMENT ACTIONS

This application's risk versus benefit assessment does not necessitate a REMS or any other risk management approach to be required by FDA.

AGENDA

1. **Introductory Comments** – 5 minutes: Welcome, Introductions, Ground rules, Objectives

2. **Discussion of Substantive Review Issues** – 45 minutes: Please refer to the background information for FDA's assessment of each issue

   A.

   B.

   C.

   

   Question to BI: What studies are ongoing or planned to evaluate efficacy in NSCLC patients whose tumors harbor uncommon EGFR mutation(s)?

   D. The site of drug substance and drug product manufacturing, a Boehringer Ingelheim facility, was inspected by FDA in November 2012. At the conclusion of this inspection, FDA's field investigator conveyed deficiencies to the representative of the facility. At this time a final compliance status has not been determined. FDA reminds you that, per 21 U.S.C. 505 (d)(3), grounds for denying approval of a pending application include finding 'the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity.'

   E. Companion Diagnostic: All outstanding issues with regard to the companion diagnostic have not been addressed. FDA is awaiting responses to information requests.

3. **Post Marketing Requirements and Commitments –** 5 minutes

   A. Post-Marketing Commitment: To submit the data from the final overall survival analysis from Study 1200.32 in order to better characterize the effects of afatinib treatment on overall survival.

4. **Major labeling issues** – 15 minutes

   A. Indication statement and limitation of use: FDA believes a limitation of use is appropriate given the small number of patients tested and apparent decrease in both progression free and overall survival in afatinib treated patients with "other" EGFR mutations.

5. **Wrap up and Action Items** – 5 minutes

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/s/

PATRICIA KEEGAN
04/23/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 17, 2013

From: Deanne Varney DOP2/OHOP/CDER

Subject: NDA 201292 Pre-Late Cycle Meeting

Attendees: Richard Pazdur, Patricia Keegan, Tony Murgo, Kun He, Jonathan Norton, Rosane Charlab Orbach, Gideon Blumenthal, Shakun Malik, Deanne Varney, Tamy Kim, Jeff Summers, Dubravka Kufrin, Whitney Helms, Jun Yang, Runyan Jin, Hong Zhao, Li Shan Hsieh, Elsbeth Chikhale, Mahesh Ramanadham, Jennifer Shen, Jim Schlick, Karen Jones

Subject: Review Late Cycle Meeting Briefing Package and discuss proposed agenda

Discussion during the meeting: The team discussed the review issues to be included in the Late Cycle Briefing Package and discussed during the Late Cycle Meeting, as follows:

1. (b) (4)
2.
3.
4. Outstanding issues from the inspection of the DS/DP manufacturing facility.
5. Outstanding issues with the companion diagnostic.
6. Post-Marketing Commitment to submit data from the final overall survival analysis from Study 1200.32.
7. Proposed limitation of use to patients with “other” EGFR mutations.

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/s/

DEANNE R VARNEY
04/19/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 201292

MID-CYCLE COMMUNICATION

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Ann Agnor
Associate Director, Regulatory Affairs
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

Dear Ms. Agnor:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Afatinib tablets, 20 mg, 30 mg, 40 mg, (b) (4)

We also refer to the teleconference between representatives of your firm and the FDA on Wednesday, February 20, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Deanne Varney, Regulatory Project Manager at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure: Mid-Cycle Communication

MID-CYCLE COMMUNICATION

Meeting Date and Time:	February 20, 2013, 10:00
Application Number:	NDA 201292
Product Name:	Afatinib
Indication:	Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test
Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Meeting Chair:	Anthony Murgo, M.D.
Meeting Recorder:	Anuja Patel on behalf of Deanne Varney

FDA ATTENDEES

Anthony Murgo, MD	Cross-Discipline Team Leader, DOP 2/OHOP
Jeff Summers, MD	Deputy Director Safety, DOP2/OHOP
Gideon Blumenthal	Clinical Team Leader, DOP 2/OHOP
Shakun Malik, MD	Clinical Reviewer, DOP 2/OHOP
Jun Yang, PhD	Clinical Pharmacology Reviewer, DCP 5/OCP/OTS
Runyan Jin, PhD	Clinical Pharmacology Reviewer, DCP 5/OCP/OTS
Hong Zhao, PhD	Clinical Pharmacology Team Leader, DCP 5/OCP/OTS
Jonathan Norton, PhD	Statistical Reviewer, OB/DBV
Kun He, PhD	Statistical Team Leader, OB/DBV
Anuja Patel, MPH	Regulatory Project Manager, DOP 2/OHOP
Monica Hughes, MS	Lead Regulatory Project Manager, DOP 2/OHOP
Karen Jones	Chief, Project Manager Staff, DOP 2/OHOP
Jennifer Shen	CDRH Reviewer
Rosane Charlab Orbach, PhD	Genomics Reviewer, OMPT/CDER/OTS/OCP/Genomics
Eric Laughner	Associate Director, Regulatory Affairs, OHOP

(b) (4)

APPLICANT ATTENDEES

Boehringer Ingelheim Pharmaceuticals, Inc. (Boehringer):

Clinical:

Mehdi Shahidi, MD	Leader Clinical Development Afatinib
Dennis O'Brien, MD	Team Member, Drug Safety

Sven Wind, PhD	Project Pharmacokineticist
Sabine Luik, MD, MBA	Sr. Vice President, Medicine & Regulatory Affairs, US Regional Medical Director, North America
Berthold Greifenberg, MD	Vice President, Clinical Development and Medical Affairs, Oncology
Gerd Stehle, Prof, MD	Oncology Therapeutic Area Head
Ellen Gold, MD	Global Safety Evaluation, Oncology
Victoria Zazulina, MD	Leader Clinical Development Afatinib NSCLC
Vikram Chand, MD	Team Member Medicine, Oncology

Nonclinical/CMC:

Christian Meissner, PhD	R&D Project Manager
James Segretario, PhD	Director, CMC Regulatory Affairs
Peter Stei, Dr. med. vet, DABT	Nonclinical Drug Safety
Alexander Schreiber, PhD	Internal CMC Consultant

Biometrics & Data Management:

James Love, M. Stat.	Project Statistician
Michael Tsianco, PhD	Vice President Biometrics/Data Management
Claude Petit, PhD	Executive Director, Biostatistics
Julie Cong, PhD	Project Statistician
Yimei Wang, MS	Statistical Programming
Daniel Massey, MSc	Statistician (external)

Regulatory:

Ann Agnor, MS	Regulatory Affairs US
Pamela Strode	Executive Director, Regulatory Affairs
Joanne Palmisano, MD	Vice President, Regulatory Affairs
David Jones, MD	Regulatory Area Lead, Oncology
Thorsten Laux , PhD	Global Regulatory Affairs Manager

Project Management:

Rainer Kleemann, Dr. med. vet.	International Project Leader

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

FDA Comments Addressed During the Mid-Cycle Communication Meeting held on February 20, 2013:

CLINICAL ISSUES

1. Oncology Drugs Advisory Committee (ODAC) for this application.

   DISCUSSION DURING TELECONFERENCE: FDA informed Boehringer that this application will not be presented to ODAC. Boehringer asked if there were specific reasons why this application would not go to an advisory committee meeting. FDA requested that Boehringer table this question until later in the teleconference after they have heard all of FDA's comments and then, if needed, seek clarification.

2. (b) (4)

   DISCUSSION DURING TELECONFERENCE: FDA stated that Study 1200.23 (Lux Lung 1) is a failed trial (b) (4)
   (b) (4)

   Boehringer had no comments or additional questions regarding this comment.

3. (b) (4)

   DISCUSSION DURING TELECONFERENCE: (b) (4)
   urthermore, the results from a supportive single arm trial 1200.22 (Lux Lung 2) show a similar objective response for 40 and 50 mg doses and increased incidence and severity of adverse events with the 50 mg dose.

   Boehringer had no comments or additional questions regarding this comment.

4. (b) (4)

   DISCUSSION DURING TELECONFERENCE: FDA informed Boehringer that the application is still under review and the Agency is engaged in internal discussion

(b) (4)

5. Update on CDRH review of companion diagnostic.

DISCUSSION DURING TELECONFERENCE: FDA provided an update on the CDRH review of the companion diagnostic and stated that the review of the PMA P120022, QIAGEN therascreen RGQ PCR Kit, is currently ongoing. In addition, FDA informed Boehringer that major deficiencies have been identified and communicated to Qiagen in writing. CDRH/OIR and QIAGEN had a telephone conference on February 15, 2013, to discuss QIAGEN's plan and timeline for submitting the requested new studies.

Boehringer acknowledged FDA's comments and requested more information regarding the deficiencies identified and the impact of those deficiencies on this application. FDA informed Boehringer that they will need to contact Qiagen regarding the deficiencies identified.

CLINICAL PHARMACOLOGY

6. Post Marketing Requirement (PMR) under consideration.

DISCUSSION DURING TELECONFERENCE: FDA informed Boehringer that the clinical pharmacology review is ongoing; however, FDA has determined a need to conduct a pharmacokinetic (PK) study in patients with severe hepatic impairment to inform appropriate dosing in this patient population.

Boehringer requested clarification as to whether the study would be a PMC or PMR. FDA confirmed that it would be a PMR.

There were no additional comments from Boehringer.

7. The potential effect of afatinib on PK of oral P-glycoprotein probe substrates.

DISCUSSION DURING TELECONFERNCE: FDA noted that the potential effect of afatinib on the PK of oral P-glycoprotein probe substrates was not addressed in this NDA application.

FDA referred Boehringer to the FDA Drug Interaction Studies (DDI) draft guidance document and stated that additional information would be requested from Boehringer.

Boehringer had no additional comments.

Additional Question Discussed During the Teleconference:

8. Boehringer asked if all of the inspections related to this application have been scheduled. FDA agreed to discuss internally and provide a follow-up response to Boehringer.

3.0 INFORMATION REQUESTS

No specific information requests were conveyed during this meeting.

4.0 ADVISORY COMMITTEE MEETING

As stated in Clinical Comment #1 above, there are no plans for this application to come to the Oncology Drugs Advisory Committee (ODAC). Following discussion of FDA's comments above, Boehringer did not ask for additional clarification for specific reasons why this application would not be taken to ODAC.

5.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

The FDA informed Boehringer that the proposed late cycle meeting date was scheduled for Tuesday, May 7, 2013, 2:30PM, EST.

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/s/

DEANNE R VARNEY
03/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 7, 2013

From: Deanne Varney, DOP2/OHOP/CDER

Subject: Midcycle Meeting Minutes: Afatinib NDA 201292

NME Application: NDA 201292

Product: Afatinib Tablets

Received Date: November 15, 2012

PDUFA Date: July 15, 2013

Sponsor: Boehringer Ingelheim

Proposed Indication: Locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutation(s) as detected by an FDA-approved test.

This midcycle meeting for NDA 201292 was a face-to-face internal FDA meeting.

Attendees included: Richard Pazdur, Patricia Keegan, Anthony Murgo, Shakun Malik, Jonathan Norton, Kun He, Runyan Jin, Jun Yang, Hong Zhao, Dubravka Kufrin, Whitney Helms, Li Shan Hsieh, Liang Zhou, Ali Al Hakim, Elsbeth Chikhale, Rosane Orbach Charlab, Mahesh Ramanadham, Jeff Summers, Jennifer Shen, Elizabeth Mansfield

SUMMARY OF REVIEW FINDINGS THUS FAR:

- A PFS improvement of 4.2 months with no improvement in OS is a clinical benefit of significant magnitude in patients with lung cancer as first-line treatment when compared to standard platinum doublet therapy
- (b) (4)
- A PFS improvement of 2.2 months over placebo, with no improvement is OS, does not represent a clinical benefit in patients with lung cancer after failure of first-line chemotherapy and a TKI
- The review team must further discuss if the label should limit the use of afatinib based on the type of mutation

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/s/

DEANNE R VARNEY
02/08/2013